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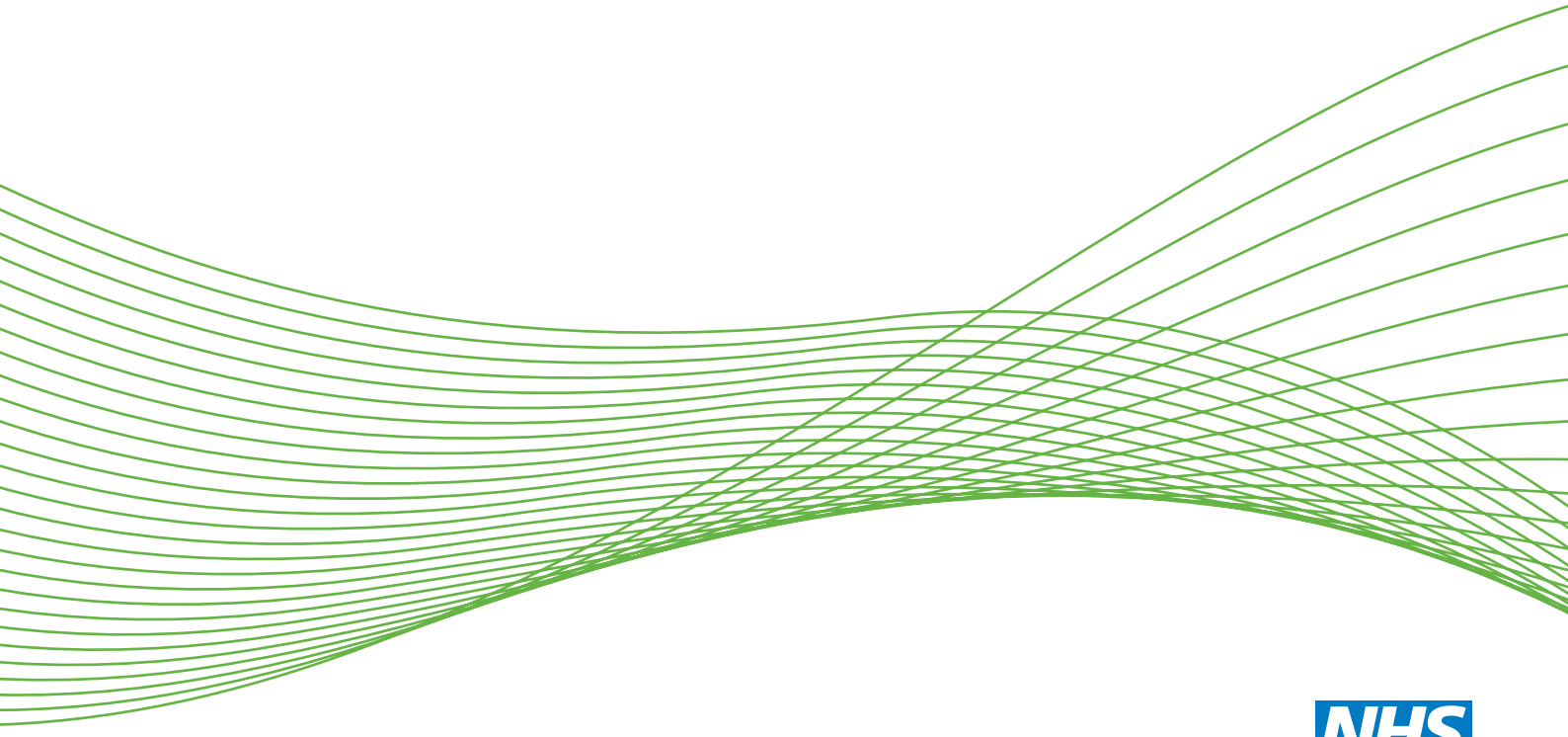

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Abstract

High-sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain: a systematic review and cost-effectiveness analysis

Marie Westwood,[1]* Thea van Asselt,[2] Bram Ramaekers,[2] Penny Whiting,[1] Praveen Thokala,[3] Manuela Joore,[2] Nigel Armstrong,[1] Janine Ross,[1] Johan Severens[4] and Jos Kleijnen[5]

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Background: Early diagnosis of acute myocardial infarction (AMI) can ensure quick and effective treatment but only 20% of adults with emergency admissions for chest pain have an AMI. High-sensitivity cardiac troponin (hs-cTn) assays may allow rapid rule-out of AMI and avoidance of unnecessary hospital admissions and anxiety.

Objective: To assess the clinical effectiveness and cost-effectiveness of hs-cTn assays for the early (within 4 hours of presentation) rule-out of AMI in adults with acute chest pain.

Methods: Sixteen databases, including MEDLINE and EMBASE, research registers and conference proceedings, were searched to October 2013. Study quality was assessed using QUADAS-2. The bivariate model was used to estimate summary sensitivity and specificity for meta-analyses involving four or more studies, otherwise random-effects logistic regression was used. The health-economic analysis considered the long-term costs and quality-adjusted life-years (QALYs) associated with different troponin (Tn) testing methods. The de novo model consisted of a decision tree and Markov model. A lifetime time horizon (60 years) was used.

Results: Eighteen studies were included in the clinical effectiveness review. The optimum strategy, based on the Roche assay, used a limit of blank (LoB) threshold in a presentation sample to rule out AMI [negative likelihood ratio (LR–) 0.10, 95% confidence interval (CI) 0.05 to 0.18]. Patients testing positive could then have a further test at 2 hours; a result above the 99th centile on either sample and a delta (Δ) of $\geq 20\%$ has some potential for ruling in an AMI [positive likelihood ratio (LR+) 8.42, 95% CI 6.11 to 11.60], whereas a result below the 99th centile on both samples and a Δ of $< 20\%$ can be used to rule out an AMI (LR– 0.04, 95% CI 0.02 to 0.10). The optimum strategy, based on the Abbott assay, used a limit of detection (LoD) threshold in a presentation sample to rule out AMI (LR– 0.01, 95% CI 0.00 to 0.08). Patients testing positive could then have a further test at 3 hours; a result above the 99th centile on

this sample has some potential for ruling in an AMI (LR+ 10.16, 95% CI 8.38 to 12.31), whereas a result below the 99th centile can be used to rule out an AMI (LR– 0.02, 95% CI 0.01 to 0.05). In the base-case analysis, standard Tn testing was both most effective and most costly. Strategies considered cost-effective depending upon incremental cost-effectiveness ratio thresholds were Abbott 99th centile (thresholds of < £6597), Beckman 99th centile (thresholds between £6597 and £30,042), Abbott optimal strategy (LoD threshold at presentation, followed by 99th centile threshold at 3 hours) (thresholds between £30,042 and £103,194) and the standard Tn test (thresholds over £103,194). The Roche 99th centile and the Roche optimal strategy [LoB threshold at presentation followed by 99th centile threshold and/or Δ20% (compared with presentation test) at 1–3 hours] were extendedly dominated in this analysis.

Conclusions: There is some evidence to suggest that hs-CTn testing may provide an effective and cost-effective approach to early rule-out of AMI. Further research is needed to clarify optimal diagnostic thresholds and testing strategies.

Study registration: This study is registered as PROSPERO CRD42013005939.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Cost-effectiveness analysis An economic analysis that converts effects into health terms and describes the costs for additional health gain.

Decision modelling A mathematical construct that allows the comparison of the relationship between costs and outcomes of alternative health-care interventions.

False-negative Incorrect negative test result – number of diseased persons with a negative test result.

False-positive Incorrect positive test result – number of non-diseased persons with a positive test result.

Incremental cost-effectiveness ratio The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.

Index test The test whose performance is being evaluated.

Likelihood ratio Likelihood ratios describe how many times more likely it is that a person with the target condition will receive a particular test result than a person without the target condition.

Markov model An analytic method particularly suited to modelling repeated events, or the progression of a chronic disease over time.

Meta-analysis Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.

Meta-regression Statistical technique used to explore the relationship between study characteristics and study results.

Opportunity costs The cost of forgone outcomes that could have been achieved through alternative investments.

Publication bias Bias arising from the preferential publication of studies with statistically significant results.

Quality-adjusted life-year A measure of health gain, used in economic evaluations, in which survival duration is weighted or adjusted by the patient's quality of life during the survival period.

Quality of life An individual's emotional, social and physical well-being and their ability to perform the ordinary tasks of living.

Receiver operating characteristic curve A graph that illustrates the trade-offs between sensitivity and specificity which result from varying the diagnostic threshold.

Reference standard The best currently available method for diagnosing the target condition. The index test is compared against this to allow calculation of estimates of accuracy.

Sensitivity Proportion of people with the target disorder who have a positive test result.

Specificity Proportion of people without the target disorder who have a negative test result.

True-negative Correct negative test result – number of non-diseased persons with a negative test result.

True-positive Correct positive test result – number of diseased persons with a positive test result.

List of abbreviations

AACC	American Association for Clinical Chemistry
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AHA	American Heart Association
AMI	acute myocardial infarction
CAD	coronary artery disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CCT	controlled clinical trial
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CHD	coronary heart disease
CI	confidence interval
CTCA	computed tomography coronary angiography
cTn	cardiac troponin
CV	coefficient of variation
DTA	diagnostic test accuracy
ECG	electrocardiography/electrocardiogram
ECLIA	electrochemiluminescence immunoassay
ED	emergency department
ESC	European Society of Cardiology
FN	false-negative
FP	false-positive
H-FABP	heart fatty acid binding protein
HES	Hospital Episode Statistics
HF	heart failure
HR	hazard ratio
hs-cTn	high-sensitivity cardiac troponin
hs-cTnI	high-sensitivity cardiac troponin I
hs-cTnT	high-sensitivity cardiac troponin T
HSROC	hierarchical summary receiver operating characteristic
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
LoB	limit of blank
LoD	limit of detection
LR–	negative likelihood ratio
LR+	positive likelihood ratio
LY	life-year
MACE	major adverse cardiac event
MeSH	medical subject heading
MI	myocardial infarction
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NPV	negative predictive value
NSTE-ACS	non-ST segment elevation acute coronary syndrome
NSTEMI	non-ST segment elevation myocardial infarction
ONS	Office for National Statistics
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
ROC	receiver operating characteristic
RR	relative risk

SE	standard error
SIGN	Scottish Intercollegiate Guidelines Network
SROC	summary receiver operating characteristic
STEMI	ST segment elevation myocardial infarction
Tn	troponin
TN	true-negative
TP	true-positive
UA	unstable angina
WHF	World Heart Federation

Plain English summary

Heart disease is a leading cause of death in the UK, with myocardial infarction (MI) (heart attack) accounting for approximately 5% of all deaths recorded in 2011. Many people attend hospital with chest pain and suspected MI; chest pain has been reported as the most common cause of hospital admissions in the UK, and 2011–12 statistics showed that it accounted for approximately 5% of all emergency admissions. It is important to diagnose people who are suspected of having a MI as early as possible in order to ensure quick and effective treatment. However, only around 20% of emergency admissions for chest pain will actually have a MI and there are many other possible causes of chest pain (e.g. gastro-oesophageal disorders, muscle pain, anxiety or stable ischaemic heart disease). Tests that can quickly tell which patients do not have MI could therefore avoid unnecessary hospital admissions and anxiety for many people.

This assessment aimed to determine the clinical effectiveness and cost-effectiveness of high-sensitivity troponin (Tn) tests, used as single tests or repeated over a short time, for diagnosing or ruling out MI in people who present to hospital with chest pain. We found that high-sensitivity Tn tests may be able to rule out MI within the 4-hour UK NHS emergency department target. Health-economic analyses indicated that high-sensitivity tests may be cost-effective compared with standard Tn tests, which require repeat testing at 10–12 hours.

Scientific summary

Background

The primary indication for this assessment is the early rule-out of acute myocardial infarction (AMI) in people presenting with acute chest pain and suspected, but not confirmed, non-ST segment elevation myocardial infarction (NSTEMI).

Cardiac troponins (cTns) I and T are used as markers of AMI. They are intended for use in conjunction with clinical history-taking and electrocardiography monitoring. Elevated troponin (Tn) levels are associated with an increased risk of adverse cardiac outcomes. However, the optimal sensitivity of standard Tn assays for AMI occurs several (10–12) hours after the onset of symptoms. Two high-sensitivity cardiac troponin (hs-cTn) assays are currently available for use in the NHS in England and Wales: ARCHITECT high-sensitivity troponin I assay (Abbott Diagnostics, Chicago, IL, USA) and the Elecsys troponin T high-sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany). One additional assay, AccuTnI+3 troponin I assay (Beckman Coulter, Brea, CA, USA), was included in the scope for this assessment pending CE marking; CE marking has now been confirmed. These assays are able to detect lower levels of Tn in the blood with analytical sensitivities up to 100 times greater than conventional Tn assays. Use of high-sensitivity assays enables the detection of small changes in Tn levels and may enable AMI to be ruled out at an earlier time after the onset of acute chest pain.

This assessment considers hs-cTn assays used singly or in series, up to 4 hours after the onset of chest pain or up to 4 hours after presentation; for serial Tn measurements, both data on change in Tn levels and peak Tn are considered.

Objective

To assess the clinical effectiveness and cost-effectiveness of high-sensitivity Tn assays for the management of adults presenting with acute chest pain, in particular for the early (within 4 hours of presentation) rule-out of AMI.

Methods

Assessment of clinical effectiveness

Sixteen databases, including MEDLINE and EMBASE, research registers and conference proceedings, were searched to October 2013. Search results were screened for relevance independently by two reviewers. Full-text inclusion assessment, data extraction and quality assessment were conducted by one reviewer and checked by a second. Study quality was assessed using QUADAS-2. The bivariate/hierarchical summary receiver operating characteristic (HSROC) model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to derive HSROC curves for meta-analyses involving four or more studies. For meta-analyses with fewer than four studies we estimated separate pooled estimates of sensitivity and specificity, using random-effects logistic regression. Summary positive likelihood ratios (LR+) and negative likelihood ratios (LR–) were derived from the summary estimates of sensitivity and specificity. Analyses were conducted separately for each of the three hs-cTn assays and were stratified according to whether or not the study evaluated the prediction of AMI or major adverse cardiac event (MACE), test timing, and the threshold used to define a positive hs-cTn result. Stratified analyses were used to investigate heterogeneity and the influence of risk of bias on summary estimates.

Assessment of cost-effectiveness

We considered the long-term costs and quality-adjusted life-years (QALYs) associated with different Tn testing methods, to diagnose or rule out NSTEMI, for patients presenting at the emergency department (ED) with suspected non-ST segment elevation acute coronary syndrome (NSTE-ACS). The de novo model consisted of a decision tree and a Markov model. The decision tree was used to model the 30-day outcomes after presentation, based on test results and the accompanying treatment decision. The long-term consequences in terms of costs and QALYs were estimated using a Markov cohort model with a lifetime time horizon (60 years). The following strategies were included in the main economic analysis:

- standard Tn at presentation and at 10–12 hours (reference standard)
- Roche Elecsys hs-cTnT at presentation: 99th centile threshold
- Roche Elecsys hs-cTnT (optimal strategy): limit of blank (LoB) threshold at presentation followed by 99th centile threshold peak within 3 hours and/or Δ20% (compared with presentation test) at 1–3 hours
- Abbott ARCHITECT hs-cTnI at presentation: 99th centile threshold
- Abbott ARCHITECT hs-cTnI (optimal strategy): limit of detection (LoD) threshold at presentation, followed by 99th centile threshold at 3 hours
- Beckman Coulter hs-cTnI at presentation: 99th centile threshold.

In the base case, it was assumed that standard Tn testing had perfect sensitivity and specificity (reference case) for diagnosing AMI and that only patients testing positive on the reference standard (standard Tn) were at increased risk for adverse events and would benefit from immediate treatment. In a secondary analysis, a proportion of patients testing positive on a hs-cTn test were treated accordingly. These patients were assumed to be treated for the hs-cTn assays and left untreated for the standard Tn test and at increased risk for adverse events. In addition, a number of sensitivity and subgroup analyses were performed.

Results

Assessment of clinical effectiveness

Eighteen studies (38 publications) were included in the review. The main potential sources of bias in the included studies related to patient spectrum and patient flow. There were also concerns regarding the applicability of the patient population and the reference standard in some of the included studies.

Diagnostic accuracy of the Roche Elecsys high-sensitivity cardiac troponin T assay (15 studies)

The most commonly evaluated testing strategy was the 99th centile threshold in a blood sample taken on presentation. Studies ($n = 6$) that excluded patients with ST segment elevation myocardial infarction (STEMI) gave a summary LR+ of 5.41 (95% CI 3.40 to 8.63) and summary LR– of 0.15 (95% CI 0.08 to 0.26) for this strategy. Estimates were similar when derived from all studies ($n = 13$) that evaluated this strategy. The optimum strategy based on this assay appeared to be one based on the combination of a LoB threshold in a presentation sample, which could be used to rule out AMI (LR– 0.10, 95% CI 0.05 to 0.18) but has limited potential to rule in an AMI (LR+ 1.83, 95% CI 1.70 to 1.97). Patients testing positive could then have a further sample taken at 2 hours; a result above the 99th centile on either the presentation or 2-hour sample and a Δ of at least 20% has some potential for ruling in an AMI (LR+ 8.42, 95% CI 6.11 to 11.60), whereas a result below the 99th centile on both samples and a Δ of $< 20\%$ can be used to rule out an AMI (LR– 0.04, 95% CI 0.02 to 0.10).

Diagnostic accuracy of the Abbott ARCHITECT high-sensitivity cardiac troponin I assay (four studies)

Three studies, all conducted in populations that included patients with STEMI, evaluated this assay at the 99th centile threshold in a blood sample taken on presentation. The summary LR+ was 11.47 (95% CI 9.04 to 16.19) and the summary LR– was 0.22 (95% CI 0.16 to 0.27). The optimum strategy appeared to be one based on the combination of a LoD threshold in a presentation sample, which could be used to rule out AMI (LR– 0.01, 95% CI 0.00 to 0.08) but has limited potential to rule in an AMI (LR+ 1.54, 95% CI 1.47 to 1.62). Patients testing positive could then have a further sample taken at 3 hours, a result above the 99th centile on this sample has some potential for ruling in an AMI (LR+ 10.16, 95% CI 8.38 to 12.31), whereas a result below the 99th centile can be used to rule out an AMI (LR– 0.02, 95% CI 0.01 to 0.05).

Diagnostic accuracy of the Beckman Coulter Access high-sensitivity cardiac troponin I (two studies)

One study, conducted in a population that included patients with STEMI, evaluated this assay at the 99th centile threshold in a blood sample taken on presentation. The summary LR+ was 3.67 (95% CI 3.26 to 4.13) and the summary LR– was 0.11 (95% CI 0.07 to 0.17). Data were not reported for the LoB/LoD threshold. There were insufficient data to determine the optimum testing strategy for this assay.

Assessment of cost-effectiveness

Base-case analysis

In the base-case analysis, standard Tn testing was both most effective and most costly. Strategies considered cost-effective depending upon incremental cost-effectiveness ratio (ICER) thresholds were Abbott ARCHITECT hs-cTnI 99th centile (thresholds of < £6597), Beckman Coulter hs-cTnI 99th centile (thresholds between £6597 and £30,042), Abbott ARCHITECT hs-cTnI optimal strategy (LoD threshold at presentation, followed by 99th centile threshold at 3 hours) (thresholds between £30,042 and £103,194), and the standard Tn test (thresholds of > £103,194). The Roche Elecsys hs-cTnT 99th centile and the Roche Elecsys hs-cTnT optimal strategy [LoB threshold at presentation followed by 99th centile threshold and/or Δ20% (compared with presentation test) at 1–3 hours] were extendedly dominated in this analysis (one of the more effective strategies was better value, in that the ICER was lower).

Secondary analysis

In the secondary analysis, which assumed that a proportion of false-positives (FPs) in the hs-cTn testing strategies had an increased risk of adverse events, standard Tn was least effective and most costly, and therefore a dominated strategy. The most effective strategy here was the Abbott ARCHITECT hs-cTnI optimal strategy. The Roche Elecsys hs-cTnT optimal strategy was extendedly dominated (one of the more effective strategies was better value in that the ICER was lower), as was the Beckman Coulter hs-cTnI 99th centile in this analysis. Strategies considered cost-effective were Abbott ARCHITECT hs-cTnI 99th centile (thresholds below £12,217), Roche Elecsys hs-cTnT 99th centile (thresholds between £12,217 and £14,992) and Abbott ARCHITECT hs-cTnI optimal strategy (thresholds over £14,992).

Sensitivity and subgroup analyses

Sensitivity analyses showed that assumptions regarding the difference between treated and untreated patients (e.g. mortality rate, risk of re-infarction) had the largest impact on relative cost-effectiveness, as well as whether or not patients testing FP were assigned treatment costs. In general, the base-case analysis was affected more by varying these assumptions than the secondary analysis. Results from the subgroup analyses led to the conclusion that hs-cTn testing is likely to be more cost-effective in younger populations, in populations with pre-existing coronary artery disease (CAD), and for patients whose symptom onset was < 3 hours ago. A no-testing strategy can be considered cost-effective only in populations with a prevalence as low as 1%.

Conclusions

Implications for service provision

There is evidence to suggest that undetectable levels of Tns (below the LoB/LoD of the assay) on presentation, measured using the Roche Elecsys hs-cTnT assay or the Abbott ARCHITECT hs-cTnI assay, may be sufficient to rule out NSTEMI in people presenting with symptoms suggestive of acute coronary syndrome (ACS). There is also evidence to suggest that, for the Roche Elecsys hs-cTnT assay and the Abbott ARCHITECT hs-cTnI assay, a further rule-out step may be possible within the 4-hour NHS ED target. There is insufficient evidence to determine an optimum testing strategy for the Beckman Coulter hs-cTnI assay. There is some limited evidence to suggest that a Tn level below the 99th centile on presentation, measured using the Roche Elecsys hs-cTnT assay, may be sufficient to rule out NSTEMI in some groups (people > 70 years old, people without pre-existing CAD and people with a clinically determined high pre-test probability).

The economic model does not provide strong evidence to prefer one hs-cTn testing strategy over another. Results do, however, indicate that hs-cTn testing in general may be cost-effective compared with standard Tn testing given that hs-cTn testing leads to cost-saving at a QALY loss. This becomes more likely if one assumes that hs-cTn testing detects some patients who require treatment despite their testing negative with standard Tn, as shown in the secondary analysis hs-cTn testing. In particular, the Abbott ARCHITECT hs-cTnI optimal strategy, which involves multiple testing and varying cut-off levels, may be promising. The main issue, with regard to service provision, if implementation of a hs-cTn testing strategy is considered, is the balance between the likely reduction in cost and the risk of a reduction in effectiveness, albeit possibly small.

Suggested research priorities

New studies are needed to evaluate fully the performance of our proposed optimal testing strategies in a clinical setting. Further research (diagnostic cohort studies or multivariable prediction modelling studies) is needed to explore fully possible variation in the performance of hs-cTn assays and the optimal testing strategies for these assays in relevant demographic and clinical subgroups (sex, age, ethnicity, renal function, previous CAD, previous AMI) and to investigate the effects of clinical judgement (assessment of pre-test probability) on test performance. As most of the uncertainties in the economic model were caused by assumptions relating to clinical effectiveness, this type of research would also facilitate economic analyses of hs-cTn testing.

Study registration

The study is registered as PROSPERO CRD42013005939.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Objective

The overall objective of this project is to assess the clinical effectiveness and cost-effectiveness of high-sensitivity troponin (Tn) assays for the management of adults presenting with acute chest pain, in particular for the early (within 4 hours of presentation) rule-out of acute myocardial infarction (AMI). The following research questions were defined to address the review objectives:

- What is the clinical effectiveness of new, high-sensitivity troponin [high-sensitivity cardiac troponin (hs-cTn)] assays (used singly or in series) compared with conventional diagnostic assessment, for achieving early discharge within 4 hours of presentation, when AMI is excluded without increase in adverse outcomes?
- What is the accuracy of new, hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) for the diagnosis of AMI in adults with acute chest pain?
- What is the accuracy of new, hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) for the prediction of major adverse cardiac events (MACEs) (cardiac death, non-fatal AMI, revascularisation or hospitalisation for myocardial ischaemia) during 30-day follow-up in adults with acute chest pain?
- What is the cost-effectiveness of using new, hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) compared with the current standard of serial Tn T and/or I testing on admission and at 10–12 hours post admission?

Chapter 2 Background and definition of the decision problem(s)

Population

The primary indication for this assessment is the early rule-out of AMI and consequent early discharge in people presenting with acute chest pain and suspected, but not confirmed, non-ST segment elevation myocardial infarction (NSTEMI). The assessment will also consider the potential effects of early diagnosis of AMI and of reduced specificity of testing.

Acute coronary syndrome (ACS) is the term used to describe a spectrum of conditions caused by coronary artery disease (CAD) [also known as coronary heart disease (CHD) or ischaemic heart disease]. ACS arises when atheromatous plaque ruptures or erodes, leading to vasospasm, thrombus formation and distal embolisation, obstructing blood flow through the coronary arteries. It incorporates three distinct conditions: unstable angina (UA), ST segment elevation myocardial infarction (STEMI) and NSTEMI. CAD and AMI are a significant health burden in the UK, with Office for National Statistics (ONS) mortality data for 2011 showing 23,705 deaths from AMI and 64,435 deaths from ischaemic heart disease; AMI accounted for approximately 5% of all deaths recorded in 2011, and ischaemic heart disease accounted for approximately 13%.[1]

People with ACS usually present with chest pain, and chest pain has been reported as the most common cause of hospital admissions in the UK;[2] Hospital Episode Statistics (HES) for 2011–12 show 243,197 emergency admissions for chest pain, accounting for approximately 5% of all emergency admissions.[3] However, many people presenting with acute chest pain will have non-cardiac underlying causes, such as gastro-oesophageal disorders, muscle pain, anxiety or stable ischaemic heart disease. A 2003 study[4] on the impact of cardiology guidelines on the diagnostic classification of people with ACS in the UK reported that the majority of people admitted to hospital with chest pain have either no ischaemic heart disease or stable ischaemic heart disease. HES for 2011–12 are consistent with this observation, showing diagnoses of AMI in 47,783 emergency admissions and UA in 32,369 admissions; this represents approximately 20% and 13% of emergency admissions with chest pain, respectively.[3] Accurate and prompt differentiation of ACS (in particular AMI), stable CAD and other causes of chest pain is therefore vital to ensure appropriate and timely intervention when required and to avoid unnecessary hospital admissions.

ST segment elevation myocardial infarction can usually be diagnosed on presentation by electrocardiogram (ECG), hence the main diagnostic challenge in the investigation of suspected ACS is the detection or rule-out of NSTEMI. Investigation of ACS can also involve identification of people with UA (CAD with worsening symptoms, but no evidence of myocardial necrosis).

Since the development of protein biomarkers of myocardial damage in the 1980s, the number of biomarker assays available has proliferated, cardiac specificity has increased, and the role of biomarkers in the diagnostic work-up of acute chest pain has expanded. Cardiac biomarkers are becoming increasingly sensitive and recent European Society of Cardiology (ESC) and American College of Cardiology (ACC) guidelines[5,6] enable AMI to be diagnosed with any rise and/or fall of Tn to above the laboratory reference range. This has resulted in fewer people being classified as having UA with no myocardial damage, and more people being classified as having NSTEMI.[7] The most recent 2 years of HES show that the number of emergency department (ED) attendances where the first recorded investigation was a cardiac biomarker rose from 13,743 in 2010–11 to 28,379 in 2011–12.[3] Cardiac troponins I and T (cTnI and cTnT), together with cardiac troponin C (cTnC), form the troponin–tropomyosin complex, which is responsible for regulating cardiac muscle contraction. cTnI and cTnT are used clinically as markers of cardiomyocyte

necrosis, indicative of AMI. Tn assays are intended for use in conjunction with clinical history-taking and ECG monitoring as, although specificity is high, Tns may also be elevated in many other conditions, including myocarditis, congestive heart failure (HF), severe infections, renal disease and chronic inflammatory conditions of the muscle or skin. Standard biochemical diagnosis of NSTEMI is based on elevation of the cardiac biomarker Tn above the 99th percentile of the reference range for the normal population.[8] Elevated Tn levels have been shown to be associated with an increased risk of adverse cardiac outcomes.[9] However, the optimal sensitivity of standard Tn assays for AMI occurs several hours after the onset of symptoms;[10] this is reflected in current clinical guidelines,[11,12] which recommend cTnI or cTnT testing at initial hospital assessment and again at 10–12 hours after the onset of symptoms. As the majority of people presenting with chest pain do not have NSTEMI, for which presentation is within a few hours of symptom onset, delayed biomarker measurement may result in unnecessary periods of extended observation or hospitalisation and associated costs. The development of cardiac biomarkers that can be used at an earlier stage without reduction in sensitivity is, therefore, desirable.

Intervention technologies

The development of hs-cTn assays means that it is possible to detect lower levels of Tn in the blood. Current generations of commercially available assays have analytical sensitivities up to 100 times greater than was the case for early Tn assays (1 ng/l vs. 100 ng/l).[13] Use of these high-sensitivity assays enable the detection of small changes in cTn levels, and may enable AMI to be ruled out at an earlier time after the onset of acute chest pain. Use of the hs-cTn assays has the potential to facilitate earlier discharge for people with normal cTn levels and earlier intervention for those with elevated levels of cTn. The recommended definition of a hs-cTn assay uses two criteria:[13,14]

- The total imprecision, coefficient of variation (CV), of the assay should be $\leq 10\%$ at the 99th percentile value of a healthy reference population.
- The limit of detection (LoD) of the assay should be such as to allow measurable concentrations to be attainable for at least 50% (ideally $> 95\%$) of healthy individuals.

A number of high-sensitivity cardiac troponin I and cardiac troponin T (hs-cTnI and hs-cTnT) assays are currently available for use in the NHS in England and Wales; all are designed for use in clinical laboratory settings.

Abbott ARCHITECT high-sensitivity troponin I assay

The Abbott ARCHITECT® hs-cTnI STAT assay (Abbott Laboratories, Chicago, IL, USA) can be used with the Abbott ARCHITECT® i2000SR and i1000SR analysers (Abbott Laboratories). The assay is a quantitative, chemiluminescent microparticle immunoassay (CMIA) for serum or plasma samples. Results are available within 16 minutes. The ARCHITECT hs-cTnI STAT assay can detect cTnI in 96% of the reference population, and has a recommended 99th percentile cut-off of 26.2 ng/l, with a CV of 4%.[15] The assay is CE marked and available to the NHS.

AccuTnI+3 troponin I assay (Beckman Coulter)

The AccuTnI+3 hs-cTnI assay is approved for use on both the Beckman Coulter Access 2 and DxI analysers (Brea, CA, USA) and has recently received CE mark approval. The assay is a quantitative, two-site paramagnetic particle chemiluminescent sandwich immunoassay for serum or plasma samples. The AccuTnI+3 assay has a recommended 99th percentile cut-off of 40 ng/l, with a CV of $< 10\%$.[16] A recent conference abstract reported data suggesting that the assay can detect cTnI in 88% of the reference population when used on the Access II analyser and in 58% of the reference population when used on the DxI analyser.[17] The same study[17] reported a difference in the 99th centile upper reference limit between the two analysers (41 ng/l for the Access II and 34 ng/l for the DxI).

Roche Elecsys high-sensitivity troponin T assay

The Roche Elecsys® cTnT-hs (high-sensitive troponin T assay) and Roche Elecsys® cTnT-hs STAT assays (Roche Diagnostics GmbH, Mannheim, Germany) can be used on the Roche Elecsys® 2010 analyser (Roche Diagnostics GmbH) and the cobas Modular Analytics e series immunoassay analysers, e411 platform. The assay is a quantitative, sandwich electrochemiluminescence immunoassay (ECLIA) for serum and plasma samples. Results are available within 18 minutes with the standard assay and within 9 minutes if the STAT assay is used. Both versions of the assay can detect cTnT in 61% of the reference population and have a recommended 99th percentile cut-off of 14 ng/l, with a CV of < 10%.[18] Both versions of the assay are CE marked and available to the NHS.

A summary of the product properties of hs-cTnI and hs-cTnT assays available to the NHS in England and Wales is provided in *Table 1*.

The hs-cTn assays can be used as single diagnostic tests, or in combination with other cardiac biomarkers, for example heart fatty acid binding protein (H-FABP) and copeptin. The use of combinations of cardiac biomarkers may increase sensitivity, when a positive result on either test is considered to be indicative of AMI, although this increase may be achieved at the expense of decreased specificity. Conversely, if a positive result on both tests is required before AMI is diagnosed, increased specificity and reduced sensitivity are likely. It is currently unclear which, if any, of the available cardiac biomarkers could add clinical benefit if used in combination with hs-cTnI and hs-cTnT, compared with hs-cTnI and hs-cTnT alone. A recent systematic review reported some data for combination testing, but none of the identified studies of Tns combined with other biomarkers used high-sensitivity methods.[7] Retrospective analysis of data from one arm of a randomised controlled trial (RCT) by the same authors provided some indication that the use of H-FABP in combination with hs-cTn, on admission, may increase sensitivity for AMI without decreasing specificity.[19] This increase was equivalent to the sensitivity achieved by serial hs-cTn testing on admission and at 90 minutes.[19] However, these tests are not readily available for analytical platforms in routine use in the NHS and discussions at the scoping stage of this assessment concluded that practical applications of H-FABP and copeptin assays and evidence for their effectiveness are not yet sufficiently developed to justify their inclusion.

This assessment will consider hs-cTn assays used singly or in series, up to 4 hours after the onset of chest pain or up to 4 hours after presentation (as reported); for serial Tn measurements, both data on change in Tn levels and peak Tn will be considered (as reported).

TABLE 1 Overview of cardiac biomarkers

Manufacturer	System	Assay	LoD (ng/l)	LoB (ng/l)	99th percentile (ng/l)[a]	CV at 99th percentile[a]	Turnaround time (minutes)[a]	CE marked
Abbott Diagnostics	ARCHITECT	STAT hs-cTnI	1.1 to 1.9	0.7 to 1.3	26.2	4%	16	✓
Beckman Coulter	Access and UniCel DxI	AccuTnI+3	10	< 10	40.0	< 10%	13	✓
Roche	Elecsys	cTnT-hs	5	3	14	< 10%	18	✓
Roche	Elecsys	cTnT-hs STAT	5	3	14	< 10%	9	✓

LoB, limit of blank.
a Information supplied to the National Institute for Health and Care Excellence (NICE) by the manufacturer.

Comparator

The comparator for this technology appraisal is the current UK standard of serial TnT and/or I testing (using any method not defined as a hs-cTn test) on admission and at 10–12 hours after the onset of symptoms.[11]

Care pathway

Diagnostic assessment

The assessment of patients with suspected ACS is described in the National Institute for Health and Care Excellence (NICE) clinical guideline 95 (CG95)[11] 'Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin'. The guideline[11] specifies that initial assessment should include a resting 12-lead ECG along with a clinical history, a physical examination and biochemical marker analysis. For people in whom a regional ST segment elevation or presumed new left branch bundle block is seen on ECG, management should follow NICE clinical guideline 167 (CG167)[20] 'The acute management of AMI with ST segment elevation'. People without persistent ST-elevation changes on ECG [i.e. with suspected non-ST segment elevation acute coronary syndrome (NSTE-ACS)], should receive further investigation using cardiac biomarkers, with the aim of distinguishing NSTEMI from UA. NICE CG95[11] makes the following recommendations on the use of cardiac biomarkers:

- Take a blood sample for cTnI or cTnT on initial assessment in hospital. These are the preferred biochemical markers to diagnose AMI.
- Take a second blood sample for cTnI or cTnT measurement 10–12 hours after the onset of symptoms.
- Do not use biomarkers such as natriuretic peptides and high-sensitivity C-reactive protein to diagnose an ACS.
- Do not use biomarkers of myocardial ischaemia (such as ischaemia-modified albumin) as opposed to markers of necrosis when assessing people with acute chest pain.
- Take into account the clinical presentation, from the time of onset of symptoms and the resting 12-lead ECG findings, when interpreting Tn measurements.

Clinical guideline 95[11] recommends that a diagnosis of NSTEMI should be made using the universal definition of AMI.[8] However, the third universal definition of AMI has been updated since the publication of CG95.[21] The most recent version states that AMI is defined as 'The detection of a rise and/or fall of cardiac biomarker values (preferably cardiac Tn) with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischaemia, new or presumed new significant ST segment T wave changes or new left branch bundle block, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy'.

The Scottish Intercollegiate Guidelines Network guideline 93 (SIGN 93)[12] provides similar recommendations on the diagnostic work-up of people with suspected ACS, stating:

- immediate assessment with a 12-lead ECG
- repeat 12-lead ECG if there is diagnostic uncertainty or change in clinical status, and at discharge
- serum Tn measurement on arrival at hospital
- repeat serum Tn measurement 12 hours after the onset of symptoms
- Tn concentrations should not be interpreted in isolation but with regard to clinical presentation.

Guidelines from the ESC[22] on the diagnostic assessment of people with a suspected NSTE-ACS are consistent with those of NICE and SIGN, but additionally acknowledge the use of high-sensitivity Tn assays and make recommendations on a fast-track rule-out protocol. The guidelines[22] state that hs-cTn assays have a negative predictive value (NPV) of > 95% for AMI on admission; including a second sample of hs-cTn at 3 hours can increase this to 100%.

Management/treatment

The NICE clinical guideline 94 (CG94), '*Unstable angina and NSTEMI: The early management of unstable angina and non-STEMI*',[23] provides recommendations on the management of people with suspected NSTE-ACS. The guideline[23] states that initial treatment should include a combination of antiplatelet (aspirin, clopidogrel and glycoprotein IIb/IIIa inhibitors) and antithrombin therapy, and should take into account contraindications, risk factors and the likelihood of percutaneous coronary intervention. SIGN 93[12] makes similar recommendations. It is recommended that people with a diagnosis of NSTEMI, who are assessed as being at low risk of future complications, receive conservative treatment with aspirin and/or clopidogrel, or aspirin in combination with ticagrelor. People at a higher risk of future complications should be offered coronary angiography (within 96 hours of admission), with subsequent coronary revascularisation by percutaneous coronary intervention or coronary artery bypass grafting where indicated.[23] Additional testing to quantify inducible ischaemia may also be used, before discharge, to identify those who may need further intervention[23] and SIGN 93[12] also recommends functional testing to identify people at higher risk. SIGN 93[12] states that people in whom an elevated Tn level is not observed may be discharged for further follow-up according to clinical judgement and, in some cases, the results of ischaemia testing.[12]

Longer-term follow-up of people who have had an AMI is described in full in NICE clinical guideline 48 (CG48)[24] 'Secondary prevention in primary and secondary care for patients following a myocardial infarction'. This includes recommendations on lifestyle changes, cardiac rehabilitation programmes, drug therapy [including a combination of angiotensin-converting enzyme (ACE) inhibitors, aspirin, beta-blockers and statins], and further cardiological assessment to determine whether coronary revascularisation is required.

Chapter 3 Assessment of clinical effectiveness

A systematic review was conducted to summarise the evidence on the clinical effectiveness of hs-cTn assays for the early rule-out or diagnosis of AMI in people with acute chest pain. Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[25] and the NICE Diagnostics Assessment Programme manual.[26,27]

Systematic review methods

Search strategy

Search strategies were based on intervention (high-sensitivity Tn assays) and target condition, as recommended in the CRD guidance for undertaking reviews in health care[25] and the Cochrane *Handbook for Diagnostic Test Accuracy Reviews*.[27]

Candidate search terms were identified from target references, browsing database thesauri [e.g. MEDLINE medical subject heading (MeSH) and EMBASE Emtree], existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches were used to generate test sets of target references, which informed text mining analysis of high-frequency subject-indexing terms using EndNote X4 reference management software (Thomson Reuters, CA, USA). Strategy development involved an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity.

The following databases were searched for relevant studies from 2005 to October 2013:

- MEDLINE (OvidSP): 2005–2013/10/wk1.
- MEDLINE In-Process Citations and Daily Update (OvidSP): up to 2013/10/1.
- EMBASE (OvidSP): 2005–2013/10/10.
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): Cochrane Library Issue 10 2005–2013/10/11.
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Cochrane Library Issue 9 2005–2013/10/11.
- Database of Abstracts of Reviews of Effects (DARE) (Wiley): Cochrane Library Issue 3 2005–July 2013.
- Health Technology Assessment (HTA) Database (Wiley): Cochrane Library Issue 3 2005–July 2013.
- Science Citation Index (SCI) (Web of Science): 2005–2013/10/14.
- Conference Proceedings Citation Index – Science (CPCI) (Web of Science): 2005–2013/10/14.
- Latin American and Caribbean Health Sciences Literature (LILACS) (Internet): 2005–2013/10/11 (http://regional.bvsalud.org/php/index.php?lang=en).
- International Network of Agencies for Health Technology Assessment (INAHTA) Publications (Internet): 2005–2013/10/15 (www.inahta.org/).
- BIOSIS Previews (Web of Knowledge): 2005–2013/10/11.
- National Institute for Health Research (NIHR) Health Technology Assessment programme (Internet): 2005–2013/10/14.
- Aggressive Research Intelligence Facility (ARIF) database (Internet): 2005–2013/10/16 (www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/index.aspx).
- Medion database (Internet): 2005–2013/10/16 (www.mediondatabase.nl/).
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet): up to 2013/10/10 (www.crd.york.ac.uk/prospero/).

Completed and ongoing trials were identified by searches of the following resources (2005 to October 2013):

- National Institutes of Health (NIH) ClinicalTrials.gov (Internet): up to 2013/10/1 (www.clinicaltrials.gov/).
- Current Controlled Trials (CCT) (Internet): up to 2013/10/10 (www.controlled-trials.com/).
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (Internet): up to 2013/10/10 (www.who.int/ictrp/en/).

No restrictions on language or publication status were applied. Date restrictions were applied based on expert advice on the earliest appearance of literature of high-sensitivity Tn assays. Searches took into account generic and other product names for the intervention. The main EMBASE strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the Canadian Agency for Drugs and Technologies in Health (CADTH) Peer Review Checklist.[28] Search strategies were developed specifically for each database and the keywords associated with high-sensitivity Tn T/I were adapted according to the configuration of each database. Full search strategies are reported in *Appendix 1*.

Electronic searches were undertaken for the following conference abstracts (selected based on advice from expert committee members):

- American Heart Association (AHA) Scientific Sessions (Internet): 2009–13 (http://my.americanheart.org/professional/Sessions/ScientificSessions/Archive/Archive-Scientific-Sessions_UCM_316935_SubHomePage.jsp).
- American Association for Clinical Chemistry (AACC) (Internet): 2009–13 (www.aacc.org/resourcecenters/meet_abstracts_archive/abstracts_archive/annual_meeting/Pages/default.aspx#).
- European Society of Cardiology (ESC) (Internet): 2009–13 (http://spo.escardio.org/abstract-book/search.aspx).

Identified references were downloaded in EndNote X4 software for further assessment and handling. References in retrieved articles were checked for additional studies. The final list of included papers was checked on PubMed for retractions, errata and related citations.[29–31]

Inclusion and exclusion criteria

Inclusion criteria for each of the clinical effectiveness questions are summarised in *Table 2*. Studies that fulfilled these criteria were eligible for inclusion in the review.

Inclusion screening and data extraction

Two reviewers (MW and PW) independently screened the titles and abstracts of all of the reports identified by searches, and any discrepancies were discussed and resolved by consensus. Full copies of all of the studies that were deemed potentially relevant were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of studies excluded at the full paper screening stage are presented in *Appendix 4*.

Studies cited in materials provided by the manufacturers of hs-cTn assays were first checked against the project reference database, in EndNote X4; any studies not already identified by our searches were screened for inclusion following the process described above.

Data were extracted on the following: study details, inclusion and exclusion criteria, participant characteristics (demographic characteristics and cardiac risk factors), target condition (NSTEMI or AMI), details of the hs-cTnT or hs-cTnI test (manufacturer, timing, and definition of positive diagnostic threshold), details of reference standard [manufacturer, timing, diagnostic threshold for conventional Tn T or I testing, clinical and imaging components of the reference standard, method of adjudication (e.g. two independent clinicians)] and test performance outcome measures [numbers of true-positive (TP), false-positive (FP), false-negative (FN) and true-negative (TN) test results]. Data were extracted by one reviewer, using a piloted, standard data extraction form and checked by a second (MW and PW); any disagreements were resolved by consensus. Full data extraction tables are provided in *Appendix 2*.

TABLE 2 Inclusion criteria

Question	What is the accuracy of hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) for the diagnosis of AMI in adults with acute chest pain?	What is the effectiveness of hs-cTn assays (used singly or in series) compared with conventional diagnostic assessment, for achieving successful early discharge of adults with acute chest pain within 4 hours of presentation?
Participants	Adults (≥ 18 years) presenting with acute 'pain, discomfort or pressure in the chest, epigastrium, neck, jaw, or upper limb without an apparent non-cardiac source'[32] attributable to a suspected, but not proven, AMI	
Setting	Secondary or tertiary care	
Interventions (index test)	Any hs-cTnT or hs-cTnI test,[a] listed in *Table 1*, hs-cTn assays (used singly or in series,[b] such that results were available within 3 hours of presentation)	
Comparators	Any other hs-cTn test, as specified above, or no comparator	Tn T or I measurement on presentation and 10–12 hours after the onset of symptoms
Reference standard	Universal definition of AMI, including measurement of Tn T or I (using any method not defined as a hs-cTn test) on presentation and 10–12 hours after the onset of symptoms in ≥ 80% of the population[c] or occurrence of MACE (any definition used in identified studies) during 30-day follow-up	NA
Outcomes[d]	Test accuracy (the numbers of TP, FN, FP and TN test results)	Early discharge (≤ 4 hours after initial presentation) without MACE during follow-up, incidence of MACE during follow-up, re-attendance at or re-admission to hospital during follow-up, time to discharge, patient satisfaction or HRQoL measures
Study design	Diagnostic cohort studies	RCTs (CCTs) will be considered if no RCTs are identified)

CCT, controlled clinical trial; FN, false-negative; FP, false-positive; HRQoL, health-related quality of life; NA, not applicable; TN, true-negative; TP, true-positive.

a A high-sensitivity assay is defined as one that has a CV of ≤ 10% at the 99th percentile value for the healthy reference population, and for which the LoD allows measurable concentrations to be attained for at least 50% of healthy individuals.

b For serial hs-cTn assays, both data on change in Tn levels and peak Tn values were considered.

c Studies that used only new diagnostic ECG changes or outcome-based MACE (cardiac death, non-fatal AMI, revascularisation or hospitalisation for myocardial ischaemia) alongside a Tn-based reference standard were eligible for inclusion.[7]

d Any estimates of the relative accuracy/effectiveness of different hs-cTnT or hs-cTnI tests were derived from direct, within-study comparisons.

Quality assessment

The methodological quality of included diagnostic test accuracy (DTA) studies was assessed using QUADAS-2.[33] Quality assessments was undertaken by one reviewer and checked by a second (MW and PW); any disagreements were resolved by consensus.

The results of the quality assessments are summarised and presented in tables and graphs in the results of the systematic review and are presented in full, by study, in *Appendix 3*.

Methods of analysis/synthesis

Sensitivity and specificity were calculated for each set of 2 × 2 data, and plotted in receiver operating characteristic (ROC) space. The bivariate/hierarchical summary receiver operating characteristic (HSROC) model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to derive HSROC curves for meta-analyses involving four or more studies.[34–36] This approach allows for between-study heterogeneity in sensitivity and

specificity, and for the trade-off (negative correlation) between sensitivity and specificity commonly seen in diagnostic meta-analyses. For meta-analyses with fewer than four studies we estimated separate pooled estimates of sensitivity and specificity, using random-effects logistic regression.[37] Heterogeneity was assessed visually using summary receiver operating characteristic (SROC) plots and statistically using the variance of logit (sensitivity) and logit (specificity), where 'logit' indicates the logistic function: the smaller these values, the less heterogeneity between studies. Summary positive and negative likelihood ratios (LR+ and LR–) were derived from the summary estimates of sensitivity and specificity. Analyses were performed in Stata 10 (StataCorp LP, College Station, TX, USA), mainly using the *metandi* command. For analyses that would not run in Stata we used MetaDiSc version 1.4 (freeware, available to download from www.hrc.es/investigacion/metadisc_en.htm).[38]

Analyses were conducted separately for each of the three hs-cTn assays. Analyses were stratified according to whether the study evaluated the prediction of AMI or MACE, timing of collection of blood sample for testing, and the threshold used to define a positive hs-cTn result. We investigated possible sources of heterogeneity using stratified analyses based on the following variables:

- population – studies included mixed populations compared with those that excluded patients with STEMI
- age > 70 years compared with age ≤ 70 years
- patients with pre-existing CAD at baseline compared with patients without pre-existing CAD
- time from symptom onset to presentation < 3 hours compared with > 3 hours
- time from symptom onset to presentation < 6 hours compared with > 6 hours
- low to moderate pre-test probability of disease compared with high pre-test probability of disease.

Stratified analyses were conducted for all time points and thresholds for which sufficient data were available. To investigate the influence of risk of bias on the studies, we restricted analyses to studies conducted in patients at low or unclear risk of bias for the two QUADAS items considered to have the greatest potential to have introduced bias into these studies: the item on patient spectrum (1) and the item on patient flow (4). As the focus of this review was the diagnosis of NSTEMI, we conducted these analyses in studies that excluded patients with STEMI. We used SROC plots to display summary estimates from the various primary and stratified analyses.

We compared the accuracy of the three different hs-cTn assays by tabulating summary estimates from analyses for common time points and thresholds assessed for all assays. Only one study[39] provided a direct comparison of all three assays. Estimates of sensitivity, specificity, and LR+ and LR– for each assay derived from this study were included in the summary tables.

Results of the assessment of clinical effectiveness assessment

The literature searches of bibliographic databases identified 6766 references. After initial screening of titles and abstracts, 261 were considered to be potentially relevant and ordered for full paper screening; of these, 35 were included in the review.[19,40–72] All potentially relevant studies cited in documents supplied by the test manufacturers had already been identified by bibliographic database searches. One additional study[73] was identified from hand-searching of conference abstracts, and two additional studies[39,74] were identified from information supplied by clinical experts. *Figure 1* shows the flow of studies through the review process, and *Appendix 4* provides details, with reasons for exclusions, of all of the publications excluded at the full paper screening stage.

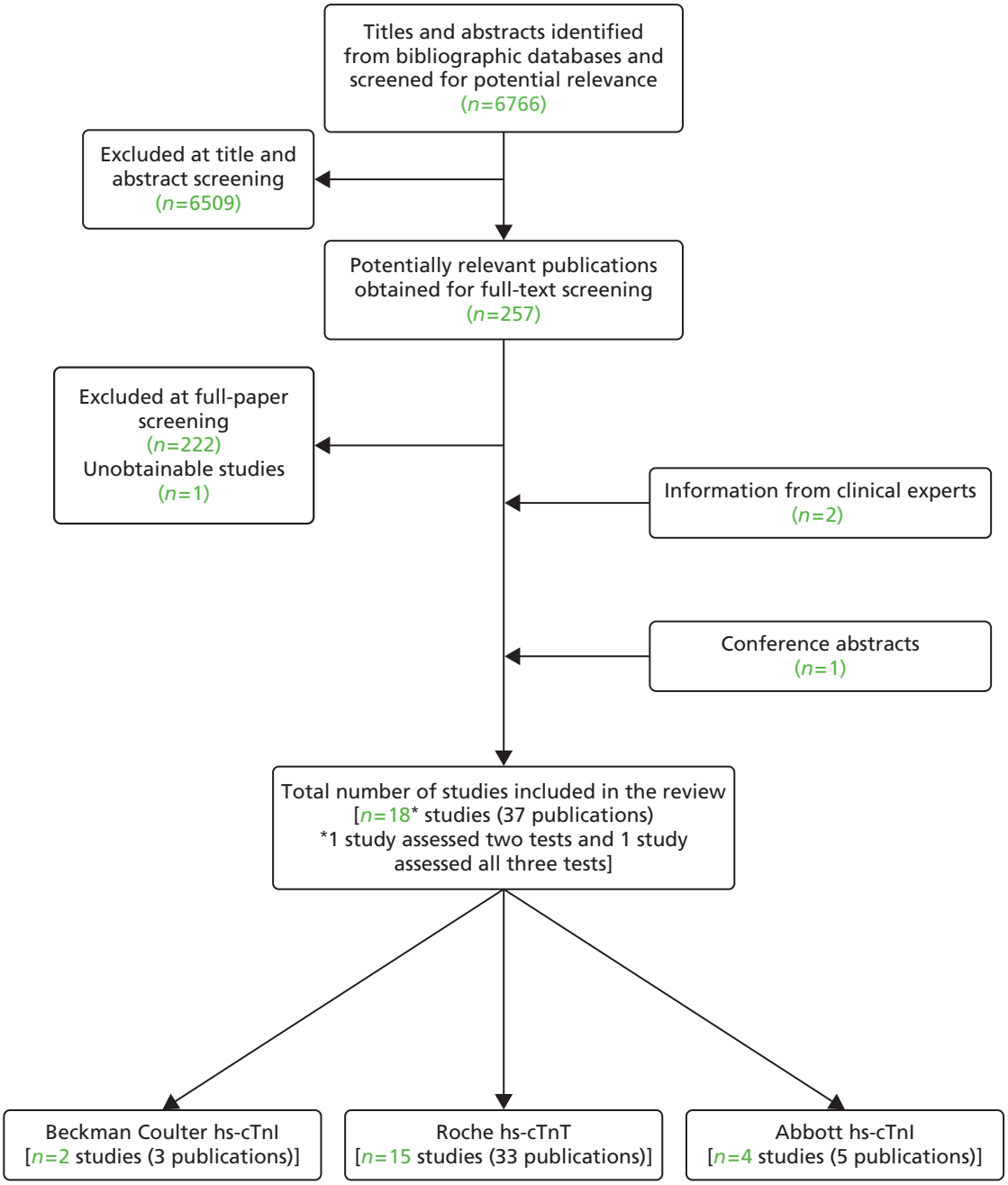

FIGURE 1 Flow of studies through the review process.

Overview of included studies

Based on the searches and inclusion screening described above, 37 publications[19,39,40–74] of 18 studies[19,39,40,42,44,46,48,49,51,54,55,57,58,63,64,67,70,73] were included in the review; the results sections of this report cites studies using the primary publication and, where this is different, the publication in which the referenced data were reported. Fifteen studies[19,39,40,42,44,46,49,51,54,55,57,58,64,67,70] reported accuracy data for the Roche Elecsys hs-cTnT assay, four studies[39,48,58,63] reported accuracy data for the Abbott ARCHITECT hs-cTnI assay, and two studies[39,73] reported accuracy data for the Beckman Coulter Access hs-cTnI assay; two studies[39,58] reported data for more than one assay. No RCTs or current controlled trials (CCTs) were identified; no studies provided data on the effects on patient-relevant outcomes of management based on hs-cTn assays within 4 hours of presentation compared with management based on standard cTn assays at presentation and after 10–12 hours. All studies included in the systematic review were diagnostic cohort studies, which reported data on the diagnostic or prognostic accuracy hs-cTn assays.

Thirteen[19,39,40,42,44,48,49,51,55,57,64,67,73] of the 18 included studies[19,39,40,42,44,46,48,49,51,54,55,57,58,63,64,67,70,73] were conducted in Europe (two in the UK[19,67]), four were conducted in Australia and New Zealand,[46,54,58,63] and one was conducted in the USA.[70] Thirteen[39,40,42,46,48,49,51,54,55,57,63,64,70] of the 18 included studies[19,39,40,42,44,46,48,49,51,54,55,57,58,63,64,67,70,73] reported receiving some support from test manufacturers, including supply of assay kits; two studies[58,73] did not report any information on funding.

Full details of the characteristics of study participants, study inclusion and exclusion criteria, and hs-cTn assay used and reference standard, and detailed results are reported in the data extraction tables presented in *Appendix 2*.

Study quality

The main potential sources of bias in the 18 studies[19,39,40,42,44,46,48,49,51,54,55,57,58,63,64,67,70,73] included in this assessment relate to patient spectrum and patient flow. There were also concerns regarding the applicability of the patient population and the reference standard in some of the included studies. The results of QUADAS-2 assessments are summarised in *Table 3* and *Figure 2*; full QUADAS-2 assessments for each study are provided in *Appendix 3*. A summary of the risks of bias and applicability concerns within each QUADAS-2 domain is provided in *Table 3*.

Patient spectrum

Three studies[42,46,51] were rated as 'high risk of bias' for patient selection and a further six[44,55,58,64,67,70] were rated as 'unclear risk of bias'. Most studies rated as 'unclear risk of bias' did not provide sufficient details to make a judgement on whether appropriate steps were taken to minimise bias when enrolling patients into the study.[44,58,64,67,70] In one study,[55] a large number of patients were not enrolled because of 'technical reasons' that were not fully defined and so it was not possible to judge whether these constituted inappropriate exclusions; this study[55] was also judged as unclear risk of bias for this domain. One study[46] enrolled patients presenting only between 05.30 and 20.00 and so patients who presented outside these hours were excluded; as these patients may differ in their presenting characteristics (e.g. time from symptom onset) this was considered to introduce a potential bias into the study. A further study[51] stated that consecutive patients were enrolled except for temporary interruptions of the study as a result of high work load in the coronary care unit. This was also considered to have the potential to lead to the inclusion of a different spectrum of patients than if consecutive patients had been enrolled. The last study[42] judged at 'high risk of bias' for patient enrolment excluded certain patient groups, including those with a Tn elevation in any two serial determinations, a prior diagnosis of ischaemic heart disease, structural heart disease, concomitant HF or significant bradyarrhythmia.

Although this assessment included studies that enrolled both mixed populations (i.e. when the target condition was any AMI) and studies restricted to populations in which patients with STEMI were excluded (i.e. target condition NSTEMI), the primary focus was the population of patients with STEMI excluded. Studies not restricted to this specific patient group were therefore considered to have high concerns regarding applicability. Seven studies[19,40,44,46,51,55,64] were restricted to patients in whom STEMI had been excluded; an additional study[39] enrolled a mixed population but also presented data for patients in whom STEMI had been excluded. Three of these studies[44,51,55] were restricted to patients admitted to coronary care/chest patients units and so were considered to represent patients with more severe disease. A further study[19] had strict inclusion criteria, which resulted in the inclusion of a very-low-risk population. These four studies[19,44,51,55] were not considered to be representative of patients with chest pain presenting to the ED, who are the main focus of this assessment, and so were also rated as having high concerns regarding applicability. Therefore, only four studies[39,40,46,75] (one[39] only for a subset of data) were considered to have low concerns regarding the applicability of the included patients.

TABLE 3 QUADAS-2 results for studies of hs-cTn assays

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Aldous (2011)[54]	☺	☺	☺	☹	☹	☺	☹
Aldous (2012)[46]	☹	☺	☺	☺	☺	☺	☹
Body (2011)[67]	?	☺	☺	☺	☹	☺	☹
Christ (2010)[57]	☺	☺	?	☺	☹	☺	☹
Collinson (2013)[19]	☺	☺	☺	☹	☹	☺	☺
Cullen (2013)[63]	☺	☺	☺	☺	☹	☺	☺
Eggers (2012)[44]	?	☺	?	☹	☹	☺	☹
Freund (2011)[49]	☺	☺	☺	☺	☹	☺	☹
Hoeller (2013)[39]	☺	☺	☺	☹	☹/☺	☺	☺
Keller (2011)[48]	☺	☺	☺	☹	☹	☺	☹
Kurz (2011)[55]	?	☺	☺	☺	☹	☺	☹
Lippi (2012)[73]	☺	☹	?	?	☹	☺	☹
Melki (2011)[51]	☹	☺	☺	☺	☹	☺	☺
Parsonage (2013)[58]	?	☺	☺	?	☹	☺	☹
Saenger (2010)[70]	?	☺	?	?	☹	☺	☹
Sanchis (2012)[42]	☹	☺	?	☺	☹	☺	☺
Santalo (2013)[40]	☺	☺	?	☺	☺	☺	?
Sebbane (2013)[64]	?	☺	☺	☹	☺	☺	☹

☺, low risk; ☹, high risk; ?, unclear risk.

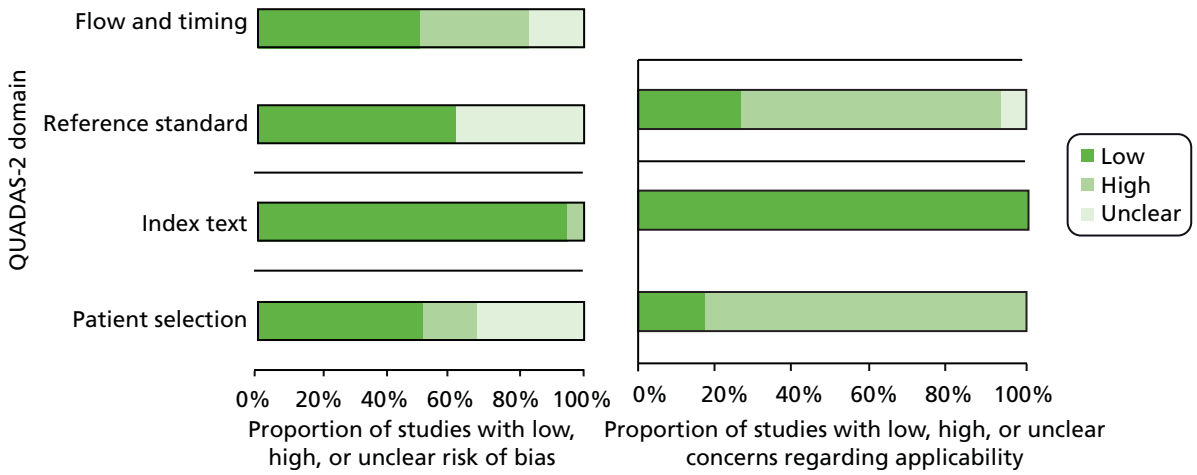

FIGURE 2 Summary of QUADAS-2 results for studies of hs-cTn assays.

Index test

All but one of the studies[19,39,40,42,44,46,48,49,51,54,55,57,58,63,64,67,70] were rated as 'low risk of bias' for the index test, as all reported data for at least one threshold that was prespecified [generally the 99th centile threshold, LoD or limit of blank (LoB) threshold]. The study[73] that was rated as high risk of bias on this domain assessed the accuracy of the Beckman Coulter Access hs-cTnI assay at a single threshold which was derived from the ROC curve. As the reference standard (diagnosis of AMI or MACE) was interpreted after the high-sensitivity Tn test, blinding was not considered important for these studies. Inclusion criteria were very tightly defined in terms of the high-sensitivity Tn assays in which we were interested and so all studies were considered to have low concerns regarding the applicability of the index test.

Reference standard

Six studies[40,42,44,55,70,71] were rated as unclear risk of bias for reference standard. In five studies,[39,41,43,54,56] this was because it was unclear whether the diagnosis of AMI/MACE was made without knowledge of the high-sensitivity Tn results. Two studies[71,74] reported as abstracts provided insufficient details on how the diagnosis of AMI was made, including whether adjudicators were blinded to the high-sensitivity Tn results, to judge whether an appropriate reference standard had been used. No studies were rated as high risk of bias for this domain, as these would not have fulfilled the inclusion criteria for the review. In our review question, we specified that an appropriate reference standard had to include a standard Tn measurement at baseline and at 10–12 hours after the onset of symptoms in 80% of the population.[11] Only five studies[19,39,42,51,63] met this criterion for standard Tn measurement and were judged to have low concerns regarding the applicability of the reference standard; all but one of the remaining studies[44,46,48,49,54,55,57,58,64,67,70,73] were judged at high risk of bias, the other study did not provide exact details on the timing of the standard Tn assay.[39]

Patient flow

Six studies[19,39,44,48,54,64] were considered at high risk of bias for patient flow and a further three studies[58,70,73] were considered at unclear risk of bias. In all cases this was related to withdrawals from the study; verification bias was not considered to be a problem in any of the studies. The three studies[58,70,71] that were rated as unclear risk of bias were reported only as abstracts and did not provide sufficient details to judge whether there were any withdrawals in the study. The studies judged at high risk of bias on this domain generally excluded patients for whom samples or high sensitive Tn results were not available.

Diagnostic accuracy of the Roche Elecsys high-sensitivity cardiac troponin T assay

Study details

Fifteen diagnostic cohort studies,[19,39,40,42,44,46,49,51,54,55,57,58,64,67,70] reported in 34 publications,[19,39,40–47,49–62,64–68,70–72,74] provided data on the diagnostic performance of the Roche Elecsys hs-cTnT assay. Fourteen[19,39,40,44,46,49,51,54,55,57,58,64,67,70] of the 15 studies[19,39,40,42,44,46,49,51,54,55,57,58,64,67,70] in this section assessed the accuracy of the Roche Elecsys hs-cTnT assay for the detection of AMI, and the remaining study[42] assessed accuracy for the prediction of MACE within 30 days of the index presentation. Eight studies[19,39,40,44,46,51,55,64] provided data specific to the population of interest for this assessment; participants with STEMI were excluded (i.e. the target condition was NSTEMI rather than any AMI).

All 14 of the studies[19,39,40,44,46,49,51,54,55,57,58,64,67,70] that assessed accuracy for the detection of AMI reported data on the diagnostic performance of a single sample taken on presentation. All but one of the studies[19,39,40,44,46,49,51,55,57,58,64,67,70] reported data for the 99th centile for the general population; the remaining study[54] reported data for a ROC-derived threshold of 9.5 ng/l. Studies additionally assessed the diagnostic performance of a LoD/LoB threshold (5 ng/l or 3 ng/l) in a single sample taken on presentation,[39,46,53,54,67] of a single sample taken 1–3 hours after presentation,[46,51] and/or the diagnostic performance of a specified change in, or peak value of, hs-cTnT level over the initial 3 hours from presentation.[39,40,46,58,70] *Table 4* provides summary estimates of the diagnostic performance of all combinations of population, diagnostic threshold and hs-cTnT test timing, which were assessed by more than one study. For analyses based on

TABLE 4 Accuracy of the Roche hs-cTnT assay: summary estimates (95% CIs)

Grouping	Population	Risk of bias	*n*	Sensitivity (%)	Specificity (%)	LR+	LR–
Presentation samples							
Any threshold[a]	All	Mixed	14	88 (84 to 91)	82 (77 to 86)	4.88 (3.84 to 6.21)	0.14 (0.11 to 0.19)
	All	Low/unclear risk of bias on patient spectrum	13	86 (83 to 89)	82 (77 to 87)	4.89 (3.76 to 6.35)	0.16 (0.14 to 0.20)
	All	Low/unclear risk of bias on patient flow	11	90 (87 to 93)	80 (77 to 84)	4.69 (3.88 to 5.66)	0.12 (0.09 to 0.16)
	All	Low/unclear risk of bias on patient spectrum and patient flow	8	89 (85 to 92)	80 (74 to 85)	4.49 (3.47 to 5.80)	0.14 (0.11 to 0.18)
99th centile threshold	All	Mixed	13	89 (85 to 92)	82 (77 to 86)	4.94 (3.84 to 6.39)	0.13 (0.10 to 0.19)
	Mixed	Mixed	8	89 (86 to 91)	81 (76 to 85)	4.64 (3.73 to 5.76)	0.14 (0.11 to 0.17)
	STEMI excluded	**Mixed**	**6**	**88 (78 to 93)**	**84 (74 to 90)**	**5.41 (3.40 to 8.63)**	**0.15 (0.08 to 0.26)**
	STEMI excluded	Low/unclear risk of bias on patient spectrum	4	81 (75 to 86)	85 (70 to 93)	5.33 (2.65 to 10.72)	0.22 (0.17 to 0.29)
	STEMI excluded	Low/unclear risk of bias on patient flow	3	92 (88 to 94)	79 (76 to 82)	4.38 (3.02 to 6.11)	0.10 (0.05 to 0.22)
	STEMI excluded	Low/unclear risk of bias on patient spectrum and patient flow	1[40]	89 (81 to 94)	71 (66 to 76)	3.11 (2.55 to 3.79)	0.15 (0.08 to 0.28)
	Age ≤ 70 years	**High risk for patient flow**	**1[19,39,53–73]**	**88 (78 to 94)**	**86 (83 to 89)**	**6.24 (5.03 to 7.74)**	**0.14 (0.07 to 0.28)**
	Age > 70 years	**High risk for patient flow**	**1[19,39,53–73]**	**97 (92 to 99)**	**49 (44 to 55)**	**1.91 (1.71 to 2.14)**	**0.05 (0.02 to 0.18)**
	Patients with pre-existing CAD	**High risk for patient flow**	**1[19,39,53–73]**	**93 (85 to 97)**	**60 (55 to 65)**	**2.32 (2.02 to 2.68)**	**0.12 (0.05 to 0.26)**

continued

TABLE 4 Accuracy of the Roche hs-cTnT assay: summary estimates (95% CIs) (*continued*)

Grouping	Population	Risk of bias	*n*	Sensitivity (%)	Specificity (%)	LR+	LR–
	Patients without pre-existing CAD	**High risk for patient flow**	**1**[19,39,47–73]	**94 (88 to 97)**	**82 (79 to 85)**	**5.18 (4.36 to 6.16)**	**0.07 (0.04 to 0.16)**
	Mixed; low to moderate pre-test probability	**Low**	**1**[49]	**89 (70 to 97)**	**85 (79 to 89)**	**5.79 (4.16 to 8.06)**	**0.13 (0.04 to 0.41)**
	Mixed; high pre-test probability	**Low**	**1**[49]	**94 (77 to 99)**	**66 (50 to 79)**	**2.78 (1.75 to 4.41)**	**0.09 (0.02 to 0.45)**
	Symptom onset < 3 hours	**1 study high risk for patient flow**	**2**[39,67–73]	**78 (71 to 83)**	**84 (81 to 86)**	**4.88 (3.91 to 5.74)**	**0.26 (0.18 to 0.39)**
	Symptom onset > 3 hours	**1 study high risk for patient flow**	**2**[39,67–73]	**94 (92 to 96)**	**77 (75 to 79)**	**4.09 (3.33 to 5.70)**	**0.08 (0.05 to 0.11)**
	Symptom onset < 6 hours	Low	1[67]	83 (74 to 89)	83 (79 to 86)	4.80 (3.80 to 6.08)	0.21 (0.14 to 0.32)
	Symptom onset > 6 hours	Low	1[67]	94 (78 to 99)	81 (75 to 86)	4.99 (3.66 to 6.81)	0.07 (0.02 to 0.34)
LoD (< 5 ng/l)	All	Mixed	3	96 (94 to 98)	41 (39 to 44)	1.63 (0.34 to 7.07)	0.10 (0.07 to 0.17)
	All; outlying study conducted in patients aged > 70 years removed	Mixed	2	95 (92 to 97)	54 (51 to 58)	2.06 (1.40 to 2.64)	0.09 (0.07 to 0.17)
	Age > 70 years	High risk for patient flow	1[19,39,53–73]	100 (95 to 100)	1 (0 to 3)	1.01 (0.99 to 1.03)	0.45 (0.02 to 8.56)
	STEMI excluded	High risk for patient spectrum	1[46]	93 (89 to 96)	58 (55 to 62)	2.20 (2.00 to 2.50)	0.11 (0.07 to 0.19)

Grouping	Population	Risk of bias	*n*	Sensitivity (%)	Specificity (%)	LR+	LR–
LoB (< 3 ng/l)	All	Mixed	3	98 (95 to 99)	40 (38 to 43)	1.63 (1.24 to 1.86)	0.05 (0.02 to 0.21)
	STEMI excluded	**High risk for patient spectrum**	**1[46]**	**95 (92 to 98)**	**48 (44 to 51)**	**1.83 (1.70 to 1.97)**	**0.10 (0.05 to 0.18)**
	Mixed; symptom onset < 3 hours	Low	1[67]	99 (94 to 100)	64 (57 to 69)	2.73 (2.31 to 3.23)	0.01 (0.00 to 0.16)
	Mixed; symptom onset > 3 hours	Low	1[67]	99 (91 to 100)	33 (28 to 38)	1.47 (1.36 to 1.59)	0.03 (0.00 to 0.47)
	Mixed; symptom onset < 6 hours	Low	1[67]	100 (96 to 100)	34 (30 to 39)	1.52 (1.41 to 1.64)	0.01 (0.00 to 0.22)
	Mixed; symptom onset > 6 hours	Low	1[67]	100 (84 to 100)	33 (27 to 40)	1.47 (1.31 to 1.65)	0.06 (0.00 to 0.91)
1–3 hours after presentation							
1–3 hours after presentation, 99th centile threshold	STEMI excluded	High risk for patient spectrum	2[46,51]	95 (92 to 97)	80 (77 to 82)	4.75 (3.98 to 5.23)	0.06 (0.00 to 0.63)
Multiple samples							
99th centile threshold (peak) and Δ20% (presentation to 3 hours)	All	High risk for patient spectrum	1[46–50]	50 (43 to 56)	94 (92 to 96)	8.40 (6.10 to 11.60)	0.54 (0.47 to 0.62)
99th centile (peak) threshold or Δ20% (presentation to 3 hours)	All	High risk for patient spectrum	1[46–50]	97 (94 to 99)	65 (61 to 68)	2.80 (2.50 to 3.10)	0.04 (0.02 to 0.10)
99th centile (peak) threshold and Δ20% (presentation to 2 hours)	**STEMI excluded**	**Low**	**1[46–50]**	**50 (43 to 56)**	**94 (92 to 96)**	**8.42 (6.11 to 11.60)**	**0.54 (0.47 to 0.62)**
99th centile (peak) threshold or Δ20% (presentation to 2 hours)	**STEMI excluded**	**Low**	**1[46–50]**	**97 (94 to 99)**	**65 (61 to 68)**	**2.76 (2.50 to 3.05)**	**0.04 (0.02 to 0.10)**

continued

TABLE 4 Accuracy of the Roche hs-cTnT assay: summary estimates (95% CIs) (*continued*)

Grouping	Population	Risk of bias	*n*	Sensitivity (%)	Specificity (%)	LR+	LR–
Peak above 99th centile	All	Mixed	2[46,50–58]	94 (91 to 97)	84 (82 to 86)	5.88 (3.56 to 10.24)	0.07 (0.04 to 0.11)
On presentation (30 minutes after arrival), and at 2, 4 and 6–8 hours or until discharge: Δ20%	STEMI excluded	Low	1[40]	99 (94 to 100)	66 (61 to 72)	2.94 (2.50 to 3.47)	0.01 (0.00 to 0.15)
On presentation and at 1 hour: Δ17%	STEMI excluded	High risk for patient flow	1[39,65]	60 (51 to 69)	72 (69 to 75)	2.15 (1.77 to 2.60)	0.55 (0.44 to 0.70)
On presentation and at 2 hours: Δ30%	STEMI excluded	High risk for patient flow	1[40,52]	64 (52 to 74)	84 (80 to 87)	3.97 (3.05 to 5.17)	0.43 (0.31 to 0.59)
On presentation and at 3 hours: Δ8 ng/l	Mixed	Low	1[70]	95 (89 to 98)	95 (91 to 97)	19.19 (10.31 to 35.72)	0.05 (0.02 to 0.12)
Prediction of MACE							
On presentation, LoB threshold	STEMI excluded	Low	1[42]	85 (74 to 92)	46 (41 to 51)	1.58 (1.37 to 1.81)	0.33 (0.18 to 0.59)

a All but one study used the 99th centile as the threshold; the remaining study used at threshold of 9.5 ng/l.
Key results, used in cost-effectiveness modelling, are highlighted in bold text.

NSTEMI patients only when sufficient data were available, sensitivity analyses that excluded studies rated as 'high risk of bias' on one or more QUADAS domains were also reported. When combinations were assessed by a single study, diagnostic performance estimates derived from that study alone are provided. Key results used in the cost-effectiveness modelling conducted for this assessment are highlighted in bold text. Full results (including numbers of TP, FP, FN and TN test results) for all studies and all data sets are provided in *Appendix 2* (*see Study results*).

Presentation samples

The summary estimates of sensitivity and specificity, where the diagnostic threshold was defined as the 99th centile for the general population, were 89% (95% CI 85% to 92%) and 82% (95% CI 77% to 86%), based on data from 13 studies;[19,39,40,44,46,49,51,54,57,58,64,68,70] the SROC curve for this analysis is shown in *Figure 3*. The LR+ and LR– were 4.94 (95% CI 3.84 to 6.39) and 0.13 (95% CI 0.10 to 0.19), respectively. These estimates were similar when the analysis was restricted to studies that excluded participants with STEMI; summary estimates of sensitivity and specificity were 88% (95% CI 78 to 93%) and 84% (95% CI 74 to 90%), respectively (SROC curve shown in *Figure 4*) and the LR+ and LR– were 5.41 (95% CI 3.40 to 8.63) and 0.15 (95% CI 0.08 to 0.26), respectively, based on six studies.[19,40,44,46,51,64] The only study[40] conducted in a population which excluded participants with STEMI, which was rated as 'low or unclear risk of bias' on all QUADAS domains, reported similar sensitivity and negative LR (see *Table 4*) to the summary estimates, but lower estimates of specificity [71% (95% CI 66% to 76%)] and LR+ [3.11 (95% CI 2.55 to 3.79)]. Results were also similar when the analysis was restricted to eight studies[39,41,49,54,57,58,67,70] with a mixed population (i.e. where the target condition was any AMI); summary estimates of sensitivity and specificity were 89% (95% CI 86% to 91%) and 81% (95% CI 76% to 85%), respectively (SROC curve shown in *Figure 5*) and the LR+ and LR– were 4.64 (95% CI 3.73 to 5.76) and 0.14 (95% CI 0.11 to 0.17), respectively. Based on these data, it is unlikely that hs-cTnT testing on a single admission sample, using the 99th centile diagnostic threshold, would be considered adequate for either rule-out or rule-in of any AMI or NSTEMI. Although there was little apparent variation in the estimates of test performance derived from the three meta-analyses described above, the result of the second analysis (studies that excluded participants with STEMI) was selected to inform our cost-effectiveness analyses, as it best matched the main population of interest for this assessment (i.e. the target condition was NSTEMI rather than any AMI). The approach of, where possible, selecting data based on a population that excluded STEMI rather than a mixed population to inform cost-effectiveness modelling was applied throughout.

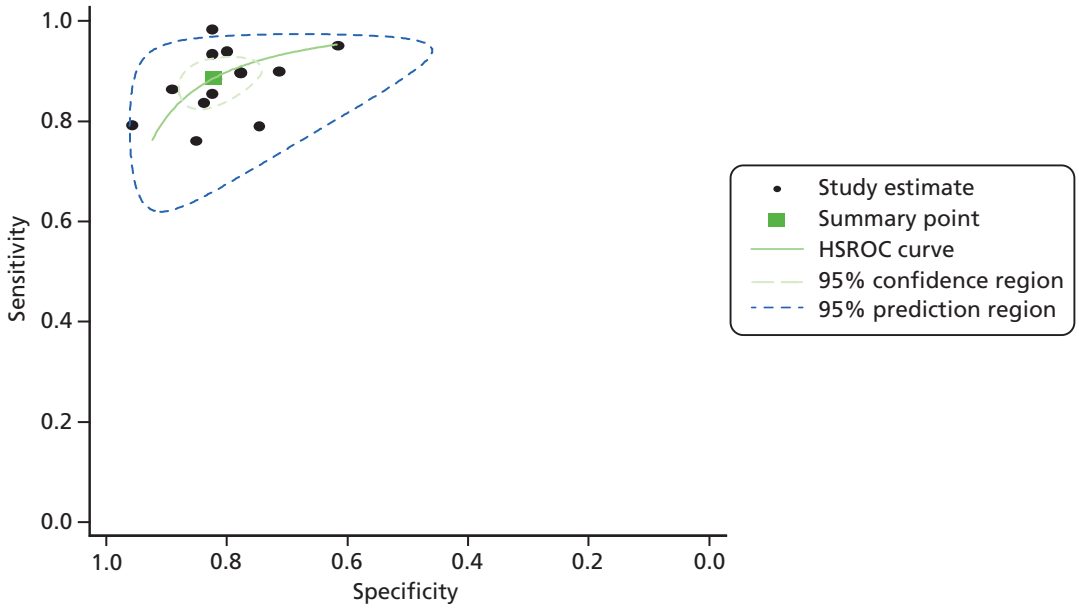

FIGURE 3 Summary receiver operating characteristic for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample (13 studies[19,39–41,46,49,51,54,57,58,64,67,70]).

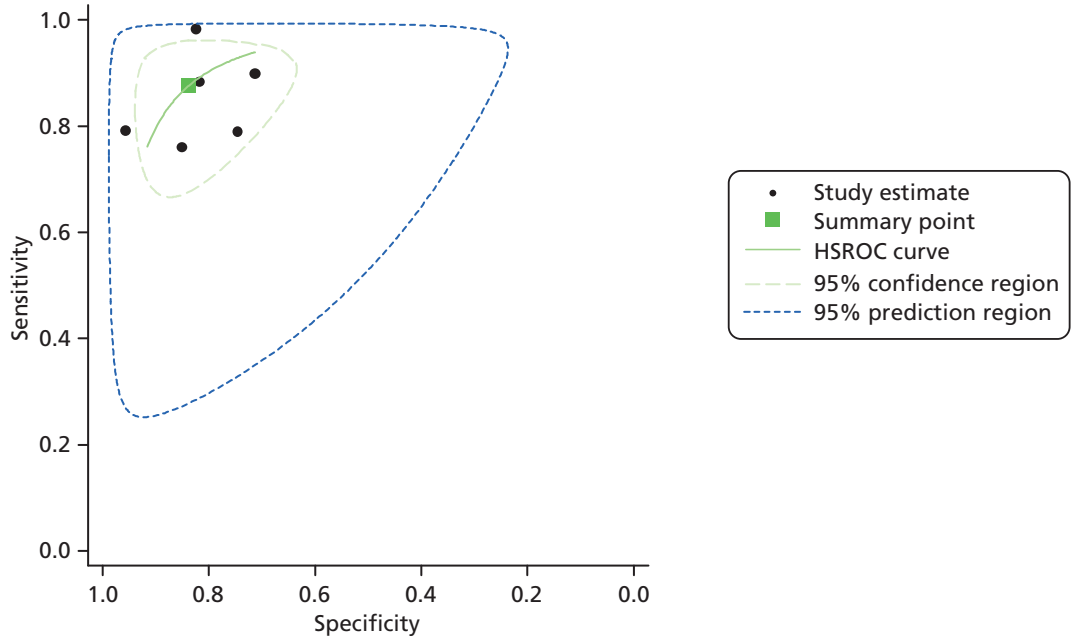

FIGURE 4 Summary receiver operating characteristic for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample (six studies[19,40,44,46,51,64] that excluded participants with STEMI).

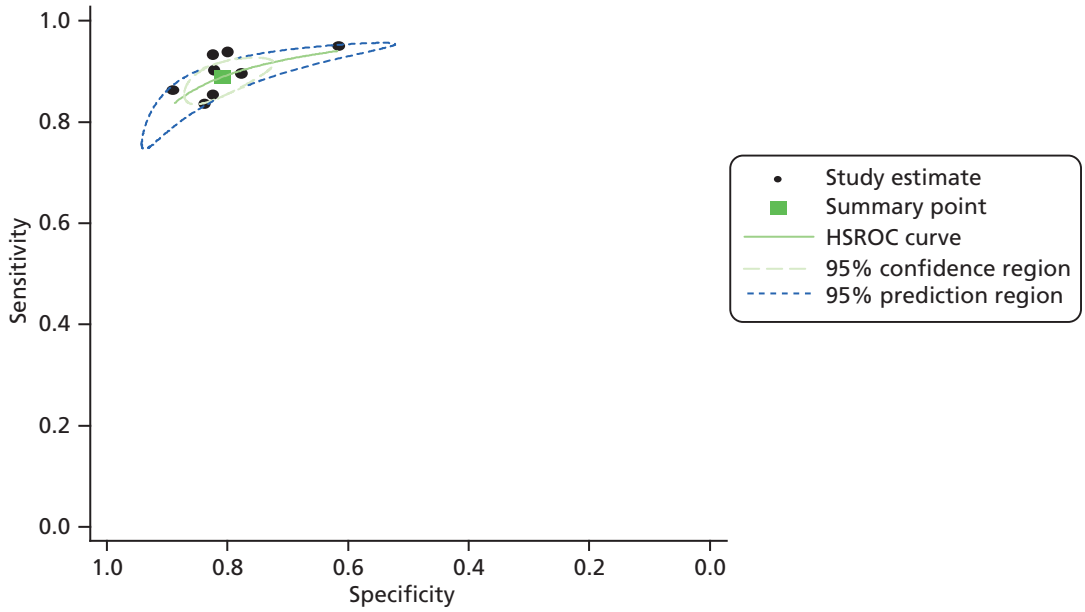

FIGURE 5 Summary receiver operating characteristic for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample (eight studies[39,41,49,54,57,58,67,70] with a mixed population, target condition any AMI).

Limited data were identified on additional clinical subgroups (age > 70 years vs. ≤ 70 years,[39,53] without pre-existing CAD compared with pre-existing CAD,[39,46] and high pre-test probability compared with low to moderate pre-test probability (determined by clinical judgement based on cardiovascular risk factors, type of chest pain, physical findings and ECG abnormalities[49]). None of these studies excluded participants with STEMI. The study that stratified participants by age[39,52] reported a higher estimate of sensitivity [97% (95% CI 92% to 99%)] and a lower estimate of LR– [0.05 (95% CI 0.02 or 0.18)] in participants > 70 years of age than for patients ≤ 70 years of age [88% (95% CI 78% to 94%) and 0.14 (95% CI 0.07 to 0.28), respectively]; the estimates of sensitivity and LR– for people > 70 years of age were also higher

and lower, respectively, than the corresponding summary estimates derived from all 13 studies[19,39,40,44,46,49,51,52,57,58,64,67,70] that used the 99th centile diagnostic threshold. A similar pattern was apparent for people with a high pre-test probability compared with those with a low to moderate pre-test probability[49] and for participants without pre-existing CAD compared with those with pre-existing CAD[39,47] (see *Table 4*). As with the age stratification, the estimates of sensitivity and LR– were higher and lower, respectively, than the corresponding summary estimates derived from all 13 studies[19,39,40,44,46,49,51,54,57,58,64,67,70] which used the 99th centile diagnostic threshold, for people with a high pre-test probability and for people without pre-existing CAD. *Figure 6* illustrates the variation in performance characteristics of a single admission sample, using the 99th centile diagnostic threshold, when used in different clinical subgroups. These data provide some indication that hs-cTnT testing on a single admission sample, using the 99th centile diagnostic threshold, may be adequate for rule-out of AMI in certain selected populations [older people (≥ 70 years), those without pre-existing CAD, and people classified by clinical judgement as having a high pre-test probability].

Time from onset of chest pain to presentation was inconsistently reported across studies; when reported, the median time from onset ranged from 2.7 hours to 8.25 hours. Full details of all information reported is provided in *Appendix 2* (see *Baseline study details*). Two studies[39,67] specifically investigated variation in test performance according to time from symptom onset to presentation. Both of these studies[39,67] were conducted in a mixed population (i.e. the target condition was any AMI). Study participants were stratified by presentation before or after 3 hours,[39,67] and before or after 6 hours.[67] Summary estimates for the 3-hour stratification indicated that a presentation sample using the 99th centile threshold had higher sensitivity [94% (95% CI 92% to 96%)] and lower specificity [77% (95% CI 75% to 79%)] for any AMI, when used to assess people presenting at > 3 hours after the onset of chest pain than when used to assess early presenters [sensitivity 78% (95% CI 71% to 83%) and specificity 84% (95% CI 81% to 86%)] (see *Table 4*). The LR– was also lower when the test was used in people presenting after 3 hours from the onset of chest pain [0.08 (95% CI 0.05 to 0.11)] than in early presenters [0.26 (95% CI 0.178 to 0.39)].

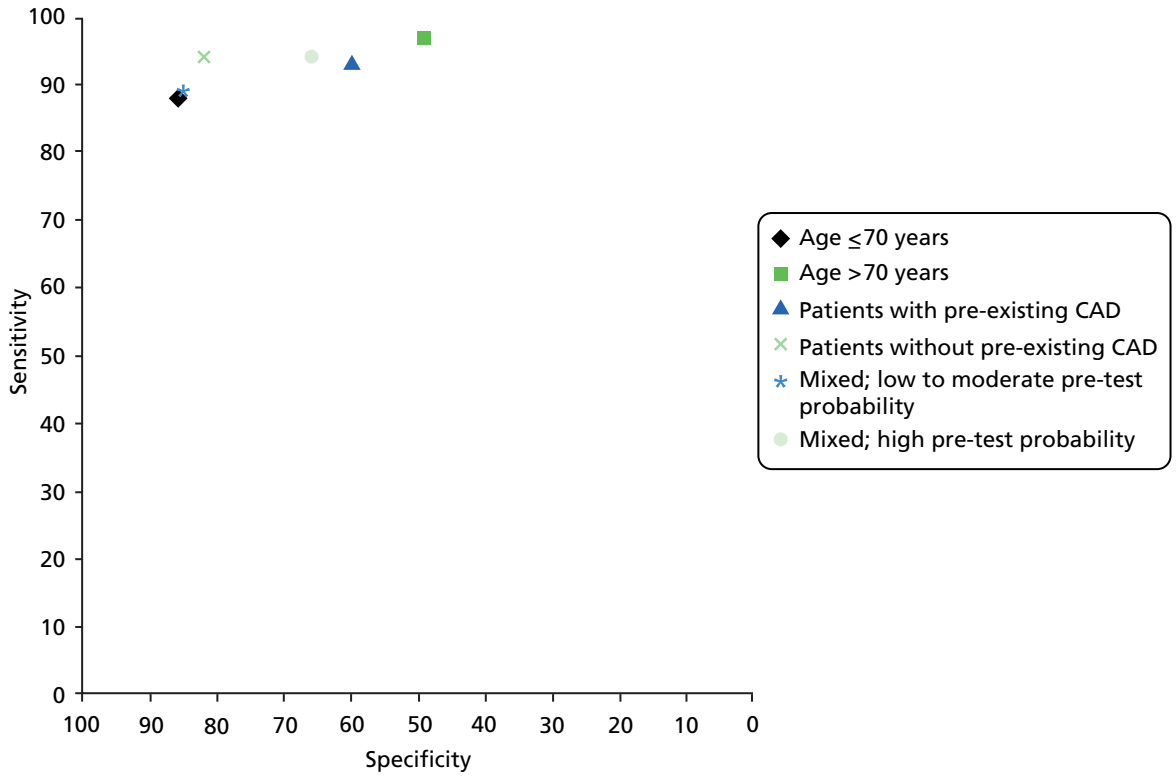

FIGURE 6 Receiver operating characteristic space plot for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample in different clinical subgroups.

Test performance in people presenting after 6 hours from the onset of chest pain was similar to that observed in people presenting after 3 hours (see *Table 4*). *Figure 7* illustrates the variation in performance characteristics of a single admission sample, using the 99th centile diagnostic threshold, when used in people presenting at different times from the onset of chest pain. These data provide some indication that hs-cTnT testing on a single admission sample, using the 99th centile diagnostic threshold, may be adequate for rule-out of AMI when people present after 3 hours from the onset of chest pain, but that longer delays in presentation did not appear to further improve rule-out performance.

Five studies[39,46,53,54,57,67] considered the performance of a presentation sample using a threshold equivalent to the LoD (5 ng/l) or LoB (3 ng/l) of the assay for the diagnosis of AMI. Three studies[39,46,53,54] reported data for the 5 ng/l threshold; one of these studies[39,52] reported data at this threshold only for participants > 70 years of age. When this study[39,52] was excluded, the summary estimates of sensitivity and specificity were 95% (95% CI 92% to 97%) and 54% (95% CI 51% to 58%), respectively, and the LR+ and LR– were 2.06 (95% CI 1.40 to 2.64) and 0.09 (95% CI 0.07 to 0.17), respectively (see *Table 4*). Three studies reported data for the 3 ng/l threshold.[42,46,67] The summary estimates of sensitivity and specificity derived from these studies were 98% (95% CI 95% to 99%) and 40% (95% CI 38% to 43%), respectively, and the LR+ and LR– were 1.63 (95% CI 1.24 to 1.86) and 0.05 (95% CI 0.02 to 0.21), respectively (see *Table 4*). Only one study[46] was conducted in a population that excluded people with STEMI; however, estimates of test performance from this study were similar to the summary estimates. For the 3-ng/l threshold, sensitivity and specificity derived from this study were 95% (95% CI 92% to 98%) and 48% (95% CI 44% to 51%), respectively, and the LR+ and LR– were 1.83 (95% CI 1.70 to 1.97) and 0.10 (95% CI 0.05 to 0.18), respectively (see *Table 4*).[46] For the 5-ng/l threshold, sensitivity and specificity derived from this study were 93% (95% CI 89% to 96%) and 58% (95% CI 55% to 62%), respectively, and the LR+ and LR– were 2.20 (95% CI 2.00 to 2.50) and 0.11 (95% CI 0.07 to 0.19), respectively (see *Table 4*).[46] These data provide some indication that hs-cTnT testing on a single admission sample may be adequate to rule out any AMI or NSTEMI, where a lower diagnostic threshold (5 ng/l or 3 ng/l) is used.

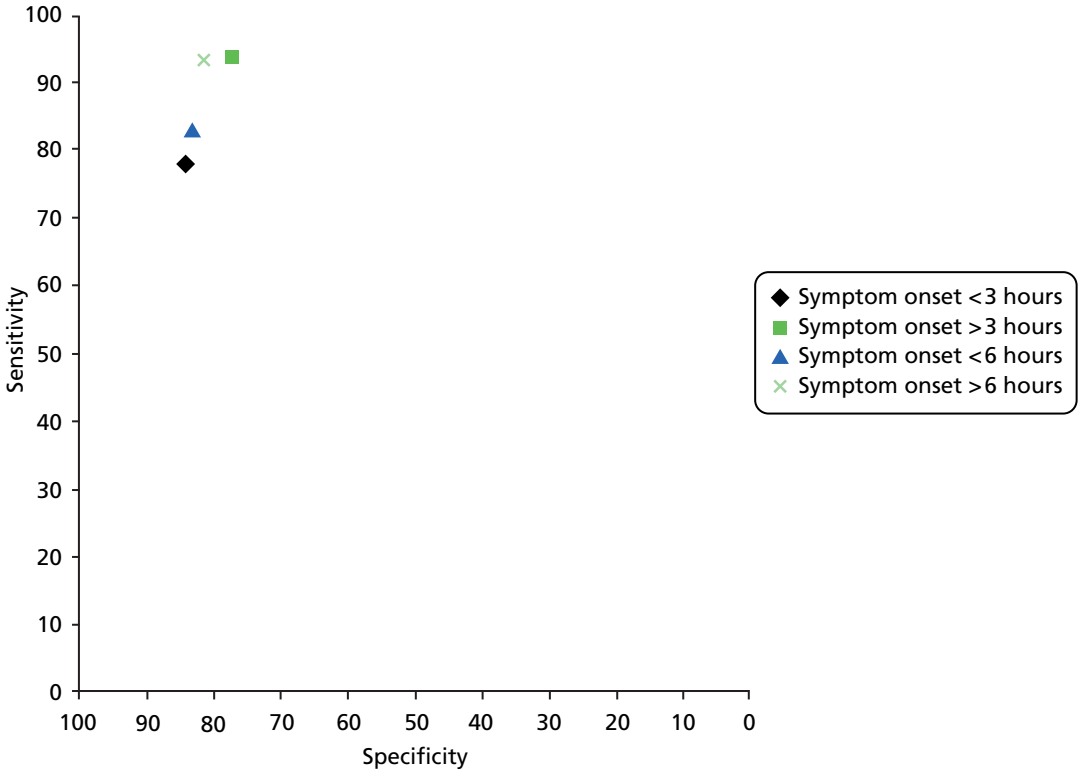

FIGURE 7 Receiver operating characteristic space plot for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample in people presenting at different times after symptom onset.

Subsequent samples

The summary estimates of sensitivity and specificity, where the diagnostic threshold was defined as the 99th centile for the general population but the sample was taken 1–3 hours after presentation, were 95% (95% CI 92% to 97%) and 80% (95% CI 77% to 82%), based on data from two studies.[46,51] The LR+ and LR– were 4.75 (95% CI 3.98 to 5.23) and 0.06 (95% CI 0.00 to 0.63), respectively (see *Table 4*). Both of these studies[46,51] were conducted in populations that excluded people with STEMI. Unsurprisingly, these data indicate a similar improvement in rule-out performance to that seen when the test is used only in people presenting > 3 hours after the onset of chest pain.

Multiple samples

Six studies[39,40,46,50,52,58,65,70] (data reported in multiple publications) provided data on the performance of a variety of diagnostic strategies involving multiple sampling, most commonly involving a combination of a peak hs-cTn value above the 99th centile diagnostic threshold and a 20% change in hs-cTnT over 2 or 3 hours following presentation (see *Table 4*). *Figure 8* shows the results of these studies plotted in ROC space. One study[46,50] reported data for this combination over 2 hours in a population that excluded people with STEMI, and this study[46,50] was used in cost-effectiveness modelling. It is important to give full consideration to the optimal way of interpreting combination data of this type. As can be seen from the values reported in *Table 4*, a positive result from the 'AND' combination (defined as both a peak value above the 99th centile AND a change of > 20% over 2 hours) provides the optimum rule-in performance [LR+ 8.42 (95% CI 6.11 to 11.60)]; conversely, a negative result from the 'OR' combination (defined as both no value above the 99th centile AND a change of < 20% over 2 hours) provides the optimum rule-out performance [LR– 0.04 (95% CI 0.02 to 0.10)]. Where a patient has a negative result from the 'AND' combination/positive result from the 'OR' combination (defined as either a peak value above the 99th centile OR a change of > 20% over 2 hours), further investigation is likely to be needed. This optimal interpretation strategy is illustrated in *Figure 9*, along with a potential initial rule-out step, based on a presentation sample below the LoB threshold (3 ng/l); this strategy is included in cost-effectiveness modelling. *Figure 9* shows the application of this two-stage approach to a theoretical cohort of 1000 people presenting with symptoms suggestive of ACS (STEMI excluded); the estimated number of people with

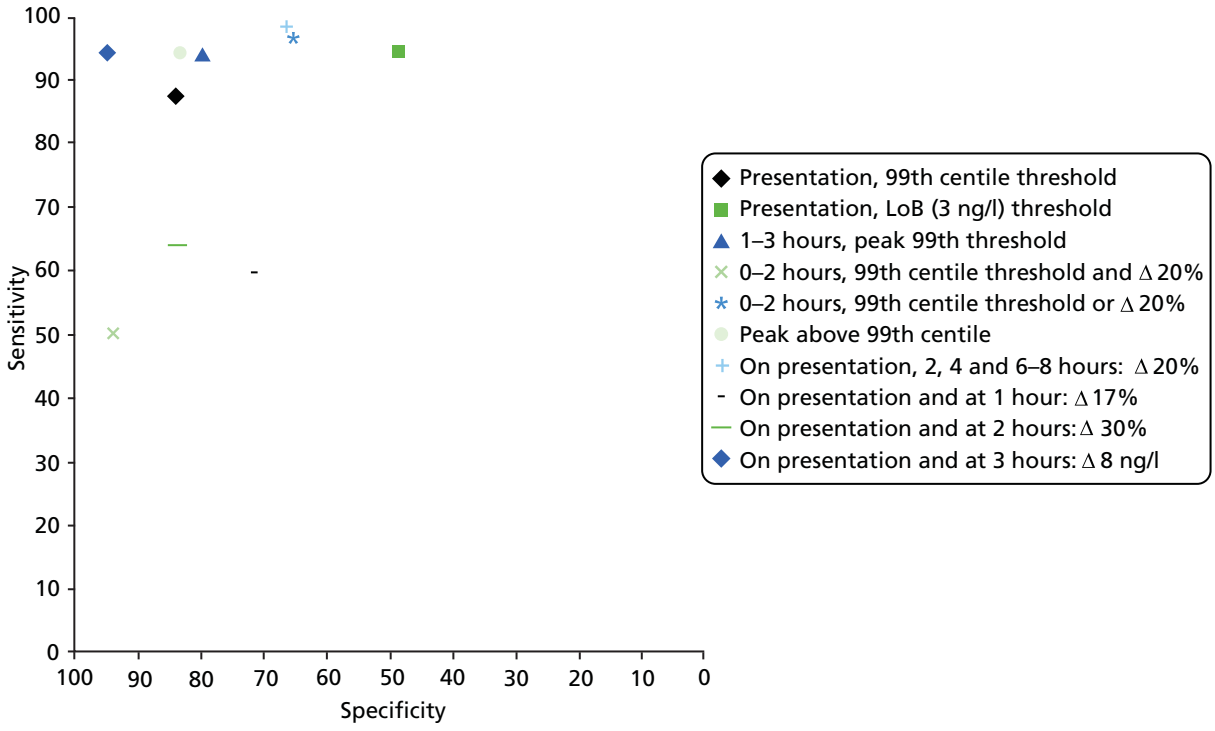

FIGURE 8 Receiver operating characteristic space plot of the Roche Elecsys hs-cTnT assay using multiple sampling strategies.

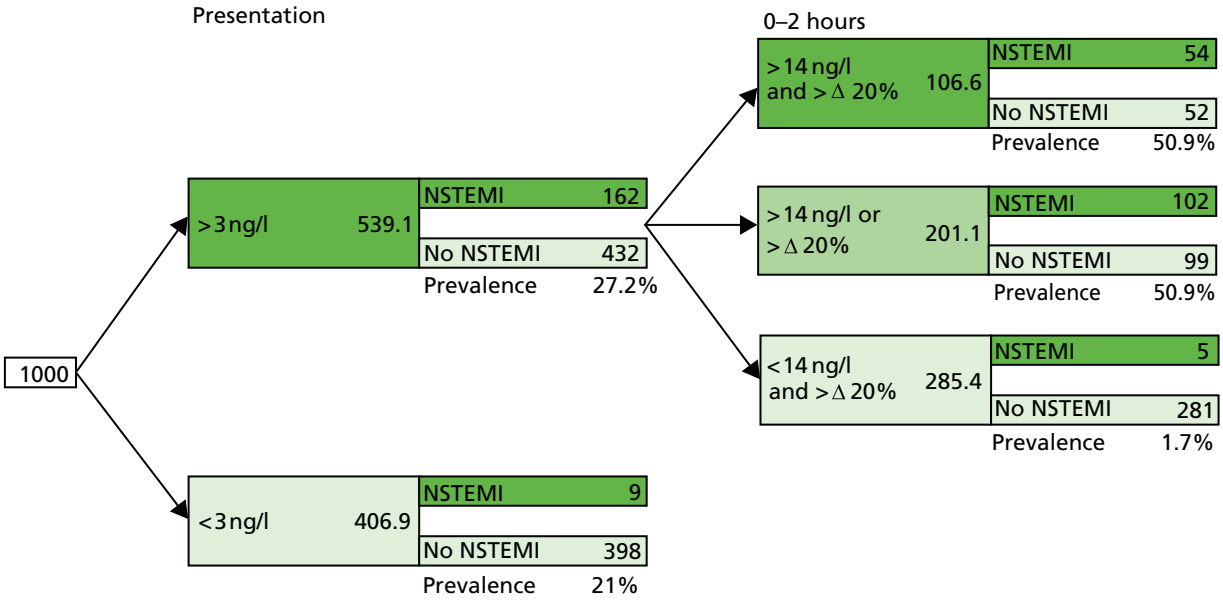

FIGURE 9 Testing pathway for the Roche Elecsys hs-cTnT assay used in cost-effectiveness modelling.

AMI and a negative test result who would be erroneously discharged based on this testing strategy is 14 (nine at the first stage and five at the second stage). The prevalence of NSTEMI was estimated to be 17%, based on data from three studies[40,46,64] conducted in populations that excluded people with STEMI. Four studies were excluded from the estimate of prevalence because they were considered to have unrepresentative populations: three studies[44,51,55] were conducted in coronary care unit populations and one study[76] was conducted in a low-risk population. It was assumed that the diagnostic performance of 'AND'/'OR' combinations of peak values of hs-cTnT and change over 2 hours, using the 99th centile diagnostic threshold, are the same for people in whom NSTEMI is not ruled out by the initial test (hs-cTnT > LoB) as for the initial population; this was because no test performance data were available for the combination of initial hs-cTnT test using the LoB diagnostic threshold followed by combined peak hs-cTnT and change over 2 hours using the 99th centile threshold.

Prognostic accuracy

One study[42] assed the performance of a presentation sample at the LoB (3 ng/l) threshold for the prediction of MACE within 30 days of the index presentation. The results of this study indicate that a positive test was a poor predictor of occurrence of MACE and a negative test was not adequate to rule out MACE within 30 days (see *Table 4*).

Diagnostic accuracy of the Abbott ARCHITECT high-sensitivity cardiac troponin I assay

Study details

Four diagnostic cohort studies[39,48,58,63] provided data on the diagnostic performance of the Abbott ARCHITECT hs-cTnI assay. Three of these studies[39,48,58] assessed the accuracy of the Abbott ARCHITECT hs-cTnI assay for the detection of AMI, and the remaining study[63] assessed accuracy for the prediction of MACE within 30 days of the index presentation. None of the studies in this section provided data specific to the population of interest for this assessment; participants with STEMI excluded (i.e. the target condition was NSTEMI rather than any AMI). All four studies[39,48,58,63] were conducted in mixed populations. Full details of the baseline characteristics of study populations, including baseline cardiac risk factors, are provided in *Appendix 2* (see *Baseline study details*).

Where a single diagnostic threshold was used to define a positive test result for AMI, all studies in this section[39,48,58,63] reported data for the 99th centile for the general population and a single sample taken

TABLE 5 Accuracy of the Abbott ARCHITECT hs-cTnI assay: summary estimates (95% CIs)

Grouping	Population	Risk of bias	*n*	Sensitivity (%)	Specificity (%)	LR+	LR–
Prediction of AMI							
Presentation samples, 99th centile threshold	**Mixed**	**Mixed**	**3**[39,48,58]	**80 (77 to 83)**	**93 (92 to 94)**	**11.47 (9.04 to 16.19)**	**0.22 (0.16 to 0.27)**
Presentation sample, LoD threshold	**Mixed**	**High risk for patient flow**	**1**[48]	**100 (98 to 100)**	**35 (32 to 38)**	**1.54 (1.47 to 1.62)**	**0.01 (0.00 to 0.08)**
3 hours after presentation, 99th centile threshold	**Mixed**	**High risk for patient flow**	**1**[48]	**98 (96 to 99)**	**90 (88 to 92)**	**10.16 (8.38 to 12.31)**	**0.02 (0.01 to 0.05)**
Presentation and 2–3 hours, peak above 99th centile threshold	Mixed	Unclear risk for patient spectrum and flow	1[58]	91 (81 to 96)	93 (91 to 95)	12.94 (9.74 to 17.19)	0.09 (0.04 to 0.23)
Above LoD threshold on admission and Δ20%	Mixed	High risk for patient flow	1[48]	82 (78 to 86)	52 (49 to 55)	1.73 (1.59 to 1.88)	0.34 (0.26 to 0.43)
On presentation and at 3 hours, Δ20%	Mixed	High risk for patient flow	1[48]	77 (72 to 82)	26 (23 to 29)	1.04 (0.97 to 1.12)	0.87 (0.69 to 1.11)
Prediction of MACE							
Presentation samples, 99th centile threshold	Mixed	High risk for patient flow for one study	2[39,63]	88 (85 to 91)	93 (91 to 94)	12.57 (8.88 to 15.35)	0.13 (0.06 to 0.28)

Key results, used in cost-effectiveness modelling, are highlighted in bold text.

at presentation. *Table 5* provides summary estimates of diagnostic performance for this testing strategy. All other combinations of diagnostic threshold and hs-cTnI test timing were assessed by only one study. *Figure 10* shows the diagnostic performance of all testing strategies assessed plotted in ROC space. Diagnostic performance estimates derived from these studies are also provided. Key results used in the cost-effectiveness modelling conducted for this assessment are highlighted in bold text. Full results (including numbers of TP, FP, FN and TN test results) for all studies and all data sets are provided in *Appendix 2* (see *Study results*).

Presentation samples

Summary estimates of sensitivity and specificity based on a diagnostic threshold defined as the 99th centile for the general population were 80% (95% CI 77% to 83%) and 93% (95% CI 92% to 94%), based on data from three studies.[39,48,58] The LR+ and LR– were 11.47 (95% CI 9.04 to 16.19) and 0.22 (95% CI 0.16 to 0.27), respectively. All three studies[39,48,58] were conducted in a mixed population (i.e. where the target condition was any AMI). Based on these data, it is unlikely that hs-cTnI testing on a single admission sample, using the 99th centile diagnostic threshold, would be considered adequate for rule-out of any AMI, but a positive test result may be useful in ruling in AMI.

No studies reported clinical subgroup data, or data on the performance of the test in people presenting at different times after symptom onset for the Abbott ARCHITECT hs-cTnI assay.

One study[48] also considered the performance of a presentation sample using the LoD of the assay as the threshold for diagnosing AMI. This study[48] provided estimates of sensitivity and specificity of 100% (95% CI 98% to 100%) and 35% (95% CI 32% to 38%), respectively, and the LR+ and LR– were 1.54 (95% CI 1.47 to 1.62) and 0.01 (95% CI 0.00 to 0.08), respectively (see *Table 5*). These data provide some indication that hs-cTnI testing on a single admission sample may be adequate to rule out any AMI, where a lower diagnostic threshold (the LoD of the assay) is used.

Subsequent samples

One study[58] assessed the performance of hs-cTnI testing on a sample taken 3 hours after presentation, where the diagnostic threshold was defined as the 99th centile for the general population. The summary estimates of sensitivity and specificity, derived from this study, were 98% (95% CI 96% to 99%) and 90% (95% CI 88% to 92%). The LR+ and LR– were 10.16 (95% CI 8.38 to 12.31) and 0.02 (95% CI 0.01 to 0.08), respectively (see *Table 5*). These data provide some indication that a sample taken at 3 hours after presentation may be informative, at the 99th centile threshold, for both rule-out and rule-in of AMI.

Multiple samples

Two studies[48,58] provided data on the performance of a variety of diagnostic strategies involving multiple sampling (see *Table 5*). None of these strategies appeared to offer a performance advantage over testing based on a single sample. *Figure 11* illustrates our proposed optimal testing pathway for the Abbott ARCHITECT hs-cTnI assay; this strategy is included in cost-effectiveness modelling. As with *Figure 9*, which presents the Roche Elecsys hs-cTnT optimal strategy, *Figure 11* shows the application of this two-stage approach to a theoretical cohort of 1000 people presenting with symptoms suggestive of ACS (STEMI excluded), with a prevalence of NSTEMI of 17%; the estimated number of people with AMI and a negative test result who would be erroneously discharged based on this testing strategy is three (zero at the first stage and three at the second stage). It was assumed that the diagnostic performance of hs-TnI using the 99th centile diagnostic threshold on a sample taken 3 hours after presentation is the same for people in whom NSTEMI is not ruled out by the initial test (hs-cTnI > LoD) as for the initial population; this was because no test performance data were available for the combination of initial hs-cTnI test using the LoD diagnostic threshold followed by 3-hour hs-cTnI and using the 99th centile threshold.

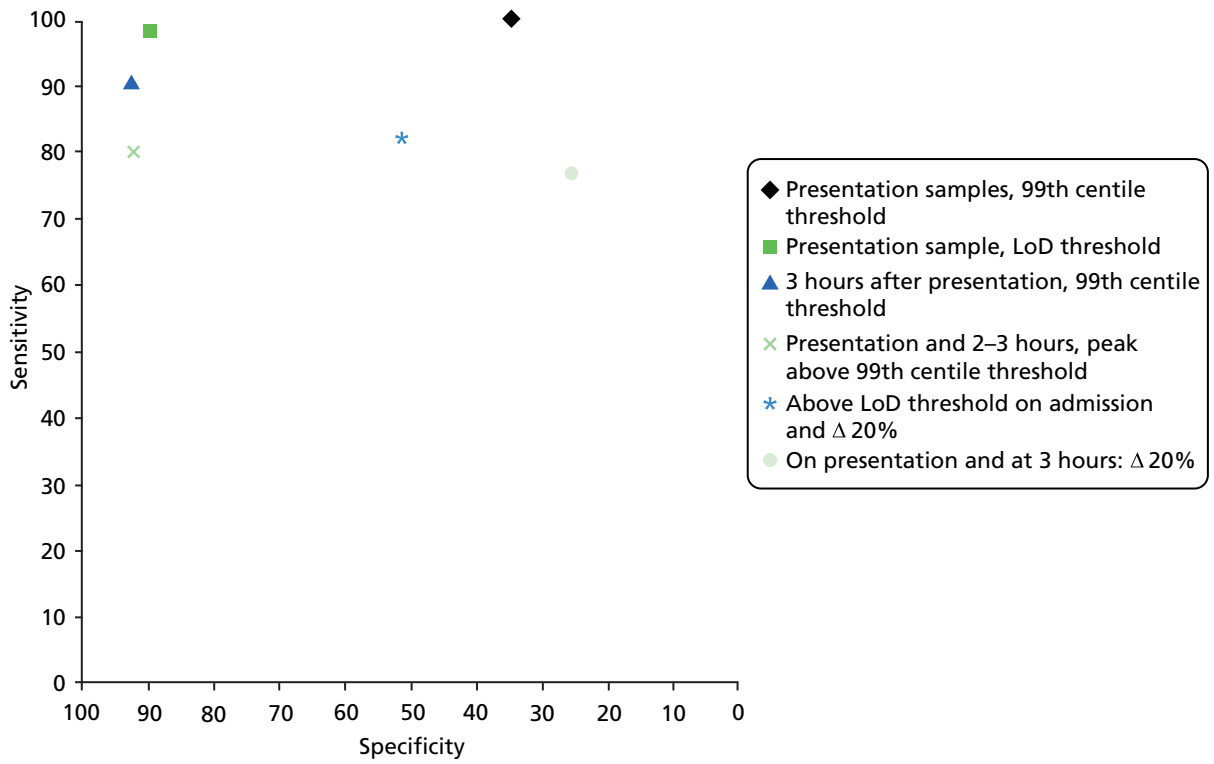

FIGURE 10 Receiver operating characteristic space plot of the Abbott ARCHITECT hs-cTnT assay.

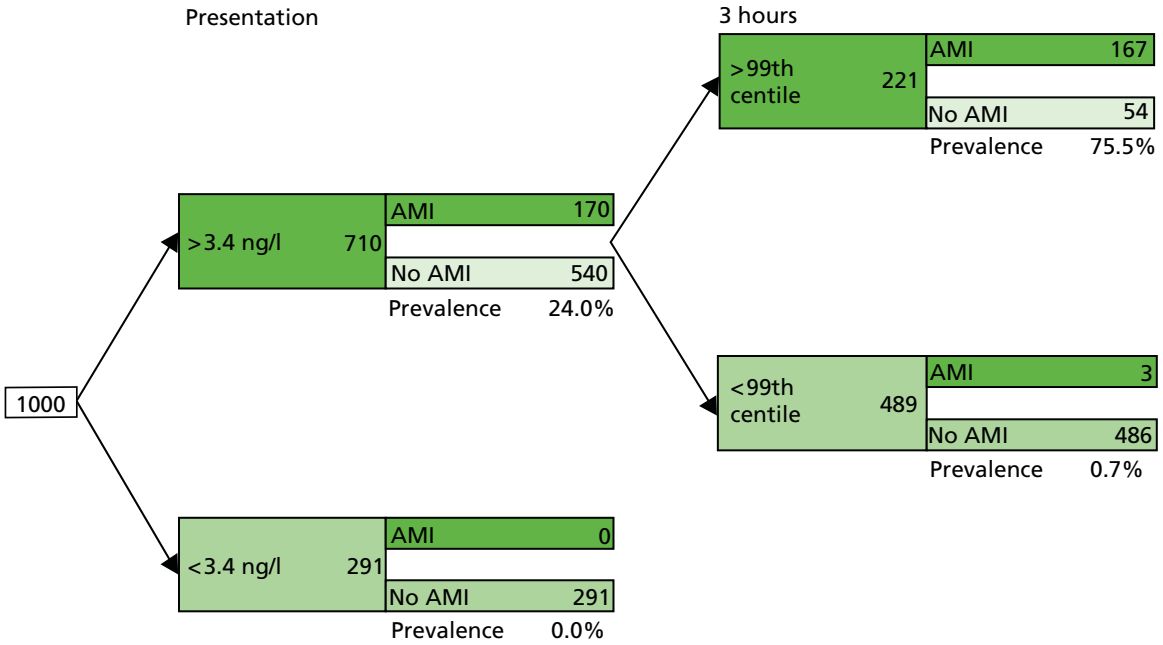

FIGURE 11 Testing pathway for the Abbott ARCHITECT hs-cTnI assay used in cost-effectiveness modelling.

Prognostic accuracy

One study[39,63] assessed the performance of a presentation sample at the 99th centile for the prediction of MACE within 30 days of the index presentation. The results of this study[39,63] indicate that a positive test may be helpful in predicting the occurrence of MACE, whereas a negative test is not adequate to rule out MACE within 30 days (see *Table 5*).

Diagnostic accuracy of the Beckman Coulter Access high-sensitivity cardiac troponin I assay

Study details

Two diagnostic cohort studies,[39,73] reported in three publications,[39,64,73] provided data on the diagnostic performance of the Beckman Coulter Access hs-cTnI assay. Both studies assessed a precommercial version of the assay and both reported accuracy data for the diagnosis of AMI (any AMI[65,73] or NSTEMI[39]). No study assessed the performance of the Beckman Coulter Access hs-cTnI assay for the prediction of MACE within 30 days of the index admission. The diagnostic performance estimates, for all combinations of diagnostic threshold and test timing assessed by included studies, are summarised in *Table 6*. *Figure 12* shows the diagnostic performance of all testing strategies assessed, plotted in ROC space.

Presentation samples

Both studies[16,39] assessed the diagnostic performance of a single sample taken at presentation. One study[39] used the 99th centile for the general population as the diagnostic threshold. This study[39] was considered to be the most relevant to our assessment and was used to inform cost-effectiveness analyses; this was the only testing strategy modelled for the Beckman Coulter Access hs-cTnI assay and, for a theoretical cohort of 1000 people presenting with symptoms suggestive of ACS (STEMI excluded) with a prevalence of NSTEMI of 17%, the estimated number of people with AMI and a negative test result who would be erroneously discharged based on this testing strategy is 14. However, it should be noted that the Beckman Coulter hs-cTnI assay evaluated in this study[39] was described as 'an investigational prototype'; the 99th centile (9 ng/l), described as 'according to the manufacturer', differs from the 99th centile given in the current product information leaflet (40 ng/l).[16] The estimates of sensitivity and specificity derived from this study were 92% (95% CI 88% to 95%) and 75% (95% CI 72% to 78%), respectively, and the LR+ and LR– were 3.67 (95% CI 3.26 to 4.13) and 0.11 (95% CI 0.07 to 0.17), respectively (see *Table 6*). The summary estimates, for the two studies[16,39] combined, were very similar (see *Table 6*).

No studies reported clinical subgroup data, or data on the performance of the test in people presenting at different times after symptom onset, for the Beckman Coulter Access hs-cTnI assay.

Subsequent samples

Neither of the studies reported data for single samples taken at time points other than presentation.

Multiple samples

One study[39] assessed the diagnostic performance of a > 27% change in hsTnI from presentation to 1 hour. This testing strategy produced results indicating a decline in both rule-in and rule-out performance compared with the single presentation sample described above (see *Table 6*).

Comparative diagnostic accuracy of the Roche Elecsys high-sensitivity troponin T assay, the Abbott ARCHITECT high-sensitivity troponin I assay and the Beckman Coulter Access high-sensitivity troponin I assay

Only one study[39] provided data for a direct comparison of the diagnostic performance of all thee hs-cTn assays in the same population. These data were for the use of the 99th centile threshold in a sample taken at presentation. This was also the only time point and threshold assessed for each study by individual included studies. As can be seen from *Tables 7* and *8*, below, the summary estimates of the performance of each test, derived from all studies reporting data for this threshold, were similar to estimates derived from the direct comparison study alone.

Selection of diagnostic strategies for inclusion in cost-effectiveness modelling

Diagnostic strategies for each hs-cTn assay were selected for inclusion in cost-effectiveness modelling based on optimal diagnostic performance as indicated by data from the systematic review. In addition, wherever possible, data from studies that excluded patients with STEMI (i.e. where the target condition was NSTEMI) were preferentially selected.

TABLE 6 Accuracy of the Beckman Coulter Access hs-cTnI assay: summary estimates (95% CIs)

Grouping	Population	Risk of bias	*n*	Sensitivity (%)	Specificity (%)	LR+	LR–
Prediction of AMI							
Presentation sample, 9 ng/l and 18 ng/l	All	High risk for patient flow on one study	2[39,73]	92 (88 to 95)	75 (72 to 77)	3.68 (2.46 to 4.48)	0.11 (0.07 to 0.16)
Presentation sample, 99th centile (9 ng/l)	**Mixed**	**High risk for patient flow**	**1[39]**	**92 (88 to 95)**	**75 (72 to 78)**	**3.67 (3.26 to 4.13)**	**0.11 (0.07 to 0.17)**
On presentation and at 1 hour: Δ27%	STEMI excluded	High risk for patient flow	1[39,63]	63 (53 to 71)	66 (63 to 69)	1.85 (1.55 to 2.21)	0.56 (0.44 to 0.72)

Key results, used in cost-effectiveness modelling, are highlighted in bold text.

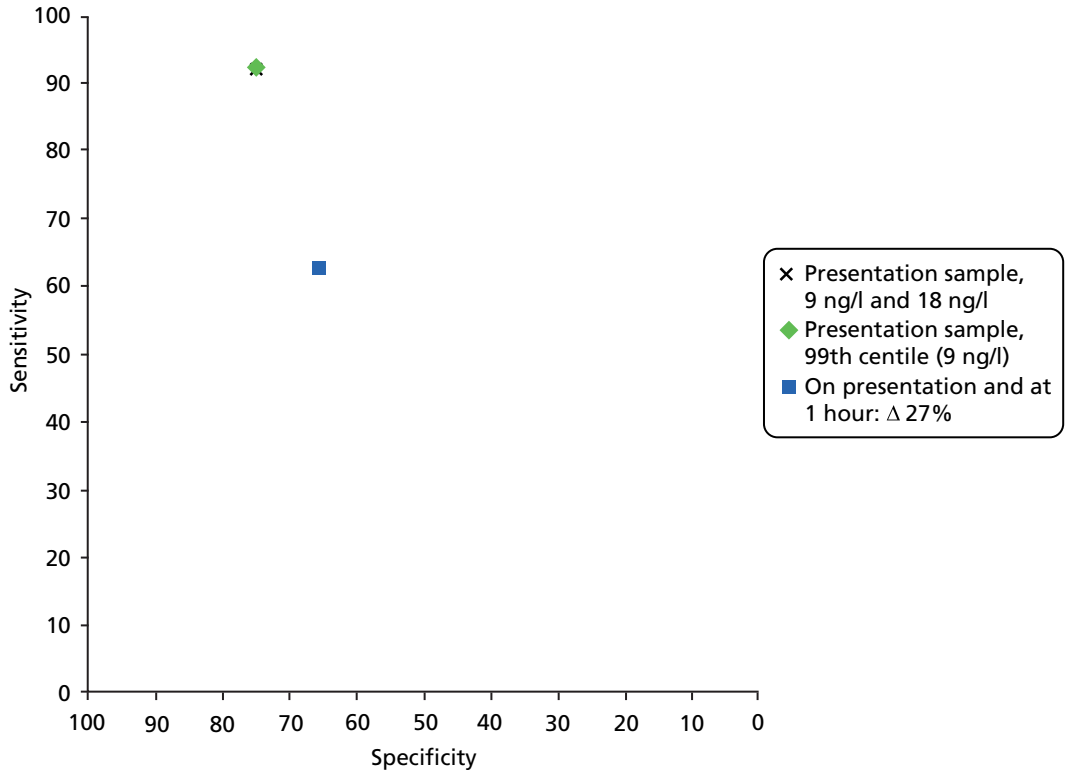

FIGURE 12 Receiver operating characteristic space plot of the Beckman Coulter Access hs-cTnI assay.

TABLE 7 Comparison between assays (presentation samples, 99th centile threshold): sensitivity and specificity (95% CI)

	Indirect comparison			Direct comparison[39]	
Assay	*n*	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Beckman Coulter Access hs-cTnI	2	92 (88 to 95)	75 (72 to 77)	92 (88 to 98)	75 (72 to 78)
Abbott ARCHITECT hs-cTnI	3	80 (77 to 83)	93 (92 to 94)	77 (72 to 82)	93 (91 to 94)
Roche Elecsys hs-cTnT	13	89 (84 to 91)	82 (77 to 86)	90 (86 to 92)	78 (76 to 79)

TABLE 8 Comparison between assays (presentation samples, 99th centile threshold): likelihood ratios (95% CI)

	Indirect comparison			Direct comparison[39]	
Assay	*n*	LR+	LR–	LR+	LR–
Beckman Coulter Access hs-cTnI	2	3.32 (2.46 to 4.48)	0.11 (0.07 to 0.16)	3.68 (3.27 to 4.14)	0.11 (0.07 to 0.17)
Abbott ARCHITECT hs-cTnI	3	12.10 (9.04 to 16.19)	0.21 (0.16 to 0.27)	10.42 (8.49 to 12.79)	0.25 (0.20 to 0.30)
Roche Elecsys hs-cTnT	13	4.96 (3.84 to 6.96)	0.14 (0.10 to 0.19)	4.02 (3.65 to 4.43)	0.13 (0.10 to 0.18)

Chapter 4 Assessment of cost-effectiveness

This chapter explores the cost-effectiveness of hs-cTn assays (used singly or in series, up to 4 hours from the onset of chest pain/presentation) compared with the current standard of serial Tn T and/or I testing on admission and at 10–12 hours after the onset of symptoms for the early rule-out of AMI in people with acute chest pain.

Review of economic analyses of high-sensitivity cardiac troponin assays

Search strategy

Searches were undertaken to identify cost-effectiveness studies of high-sensitivity TnT/I. As with the clinical effectiveness searching, the main EMBASE strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the Canadian Agency for Drugs and Technologies in Health (CADTH) Peer Review Checklist.[28] Search strategies were developed specifically for each database and keywords associated with high-sensitivity TnT/I were adapted according to the configuration of each database. Full search strategies are reported in *Appendix 1*.

The following databases were searched for relevant studies from 2005 to October 2013:

- MEDLINE (OvidSP): 2005–2013/10/wk1.
- MEDLINE In-Process & Other Non-Indexed Citations and Daily Update (OvidSP): up to 2013/10/1.
- EMBASE (OvidSP): 2005–2013/10/17.
- NHS Economic Evaluation Database (NHS EED) (Wiley): Cochrane Library Issue 3 2005 to July 2013.
- Health Economic Evaluation Database (HEED) (Wiley): 2005–2013/10/18.
- EconLit (EBSCO): 2005–2013/09/01.
- Science Citation Index (SCI) (Web of Science): 2005–2013/10/21.
- Conference Proceedings Citation Index – Science (CPCI) (Web of Science): 2005–2013/10/21.
- Research Papers in Economics (REPEC) (Internet): up to 2013/10/21 http://repec.org/.

Identified references were downloaded in EndNote X4 software for further assessment and handling.

References in retrieved articles were checked for additional studies.

Inclusion criteria

Studies reporting a full economic analysis, which related explicitly to the cost-effectiveness of hs-cTn or standard cTn (with cTn implying either cTnI or cTnT) testing, with survival and/or quality-adjusted life-years (QALYs) as an outcome measure, were eligible for inclusion. Specifically, one of the strategies had to include cTn testing. Studies that reported only a cost-analysis of cTn testing were not included in the review.

Quality assessment

Full cost-effectiveness studies were appraised using the Drummond checklist.[77]

Results

The literature search identified 152 reports. After initial screening of titles and abstracts, five reports[7,19,78–80] were considered to be potentially relevant: two full papers[79,80] and three HTA reports.[7,19,78] Two additional reports[81,82] were provided by a clinical expert: a Canadian optimal use report[82] (similar to an HTA report) and an abstract[81] that was referred to in this report. All seven identified reports[7,19,78–82] fulfilled inclusion criteria based on full-text assessment. The seven publications related to five studies. *Figure 13* shows the flow of studies through the review process, *Table 9* lists the study details and the results of the quality assessment are shown in *Table 10*.

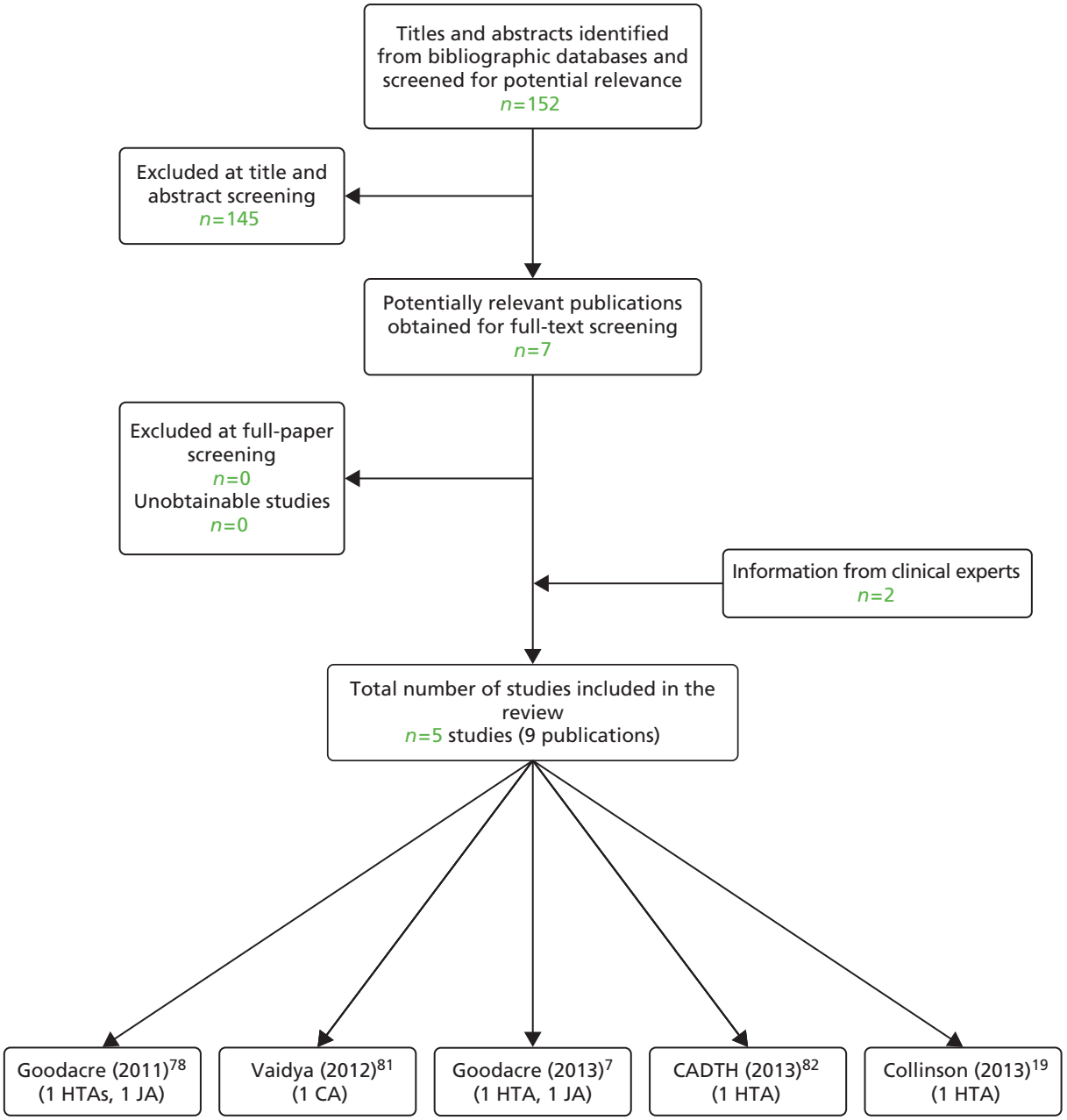

FIGURE 13 Flow of studies through the review process. CA, conference abstract; HTA, Health Technology Assessment; JA, journal article.

TABLE 9 Summary of included full papers

Study details	Goodacre *et al.*[78] and Fitzgerald *et al.*[79]	Vaidya *et al.*[81]	Thokala *et al.*[80] and Goodacre *et al.*[7]	CADTH report[82]	Collinson *et al.*[19]
Population	People presenting to hospital with chest pain attributable to suspected but not proven AMI, and no other potentially serious alternative pathology or comorbidity	Patients presenting to the hospital with chest pain	Patients attending hospital with symptoms suggesting MI, but a normal or non-diagnostic ECG, and no major comorbidities requiring hospital treatment	65-year-old patients presenting to an ED with ischaemic chest pain, without ST segment elevation ECG, who require cTn testing for diagnosis of NSTEMI	Patients presenting to hospital with symptoms suggestive of MI but with no diagnostic ECG changes (ST deviation > 1 mm or T-wave inversion > 3 mm), no known history of CHD and no major comorbidities requiring inpatient treatment
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime
Objective	Estimate the cost-effectiveness of the point-of-care panel in terms of mean costs and QALYs accrued compared with standard care	Assess the cost-effectiveness of a hs-CTnT assay, alone or combined with the H-FABP assay in comparison with the conventional cTn (cTnT) assay for the diagnosis of AMI	Estimate the incremental cost per QALY of delayed Tn testing compared with presentation testing and no testing to determine which diagnostic strategy should be recommended	To investigate the cost-effectiveness of hs-cTnT and hs-cTnI assays compared with each other, as well as with cTnI assays in patients with suspected ACS symptoms in the ED	Assess the cost-effectiveness of measuring a combination of biomarkers compared with measurement of cTn alone
Source of effectiveness information	Data from within the trial up to 3 months, and beyond this, lifetime costs and QALY estimates were used from a previous economic evaluation	No information	Sensitivity and specificity were taken from the meta-analysis as reported in the 2013 Goodacre report;[7] the RATPAC trial[19] was used for sampling patient characteristics; Mills *et al.*[83] for risk of re-infarction and death, Polanczyk *et al.*[84] for life expectancy of patients with MI and re-MI	Sensitivity and specificity from review performed in same report. Proportion UA and mortality estimated based on published studies, and one unpublished study. Utility decrements based on published study	Sensitivity and specificity data derived from data from the HTA (RATPAC) itself, short-term survival and probability of re-infarction based on Mills *et al.*[83] Source for long-term survival and QALYs not specified

continued

TABLE 9 Summary of included full papers (*continued*)

Study details	Goodacre *et al.*[78] and Fitzgerald *et al.*[79]	Vaidya *et al.*[81]	Thokala *et al.*[80] and Goodacre *et al.*[7]	CADTH report[82]	Collinson *et al.*[19]
Comparators	Diagnostic assessment using the point-of-care biochemical marker panel Conventional diagnostic assessment without the panel	Conventional cTnT hs-cTnT hs-cTnT combined with H-FABP	No biochemical testing: discharge all patients without treatment (hypothetical) Standard Tn assay measured at presentation using the 10% CV as the threshold for positivity Standard Tn assay measured at presentation using the 99th percentile threshold High-sensitivity Tn assay measured at presentation using the 99th percentile threshold Standard Tn assay measured at presentation and 10 hours after symptom onset using the 99th percentile threshold	hs-cTnT hs-cTnI cTnI	No testing: discharge all patients without treatment hs-cTn at presentation: discharge home if test is negative or admit to hospital for Tn testing at 10–12 hours if positive hs-cTn and a combination of cytoplasmic or neurohormone biomarkers at presentation: discharge home if both tests are negative or admit to hospital for Tn testing at 10–12 hours if either test is positive hs-cTn at presentation and at 90 minutes as in the RATPAC protocol: discharge home if both tests are negative or admit to hospital for Tn testing at 10–12 hours if either test is positive Standard Tn testing at 10–12 hours

Study details	Goodacre *et al.*[78] and Fitzgerald *et al.*[79]	Vaidya *et al.*[81]	Thokala *et al.*[80] and Goodacre *et al.*[7]	CADTH report[82]	Collinson *et al.*[19]
Unit costs	Microcosting study within RATPAC; PSSRU unit costs	No information	Admission and treatment were based on the national tariff Lifetime costs for MI patients were taken from Ward *et al.*[85] The price of a Tn test was taken from the 2011 Goodacre report[78]	Costs of hospital admission were based on the Ontario Case Costing Initiative database and the Ontario Schedule of Benefits for Physician Services Costs of ED visits were based on a hospital in Southwestern Ontario and the Ontario Schedule of Benefits Unit prices of cTn tests were based on information provided by the manufacturers	Hospital stay and treatment for MI based on NHS reference cost, biochemical testing based on Goodacre *et al.*[78]
Measure of benefit	QALY	AMI survivor	QALY	QALY	QALYs
Study type	Trial-based economic evaluation up to 3 months, decision tree lifetime. Cost–utility analysis	Model-based cost-effectiveness and cost–utility study	Model-based cost–utility analysis	Model-based cost–utility analysis	Model-based cost–utility study
Model assumptions	2-hour delay between sampling and results available 4 hours after presentation at ED patients moves to inpatient department 1 hour delay between presentation and start biomarker sampling After short term (test-treatment-outcome), progress only depends on whether or not patient had MI, and whether or not this was treated	No information	10 hours' Tn testing has perfect sensitivity and specificity (as it is the reference standard) 2-hour delay from the time at which sampling could be performed to results available For presentation testing strategies: decision made within 1 hour of results available For 10 hours testing strategies: decision made according to scenario applied Diagnostic strategy influences outcomes only among patients with MI	Non-NSTEMI patients are further classified into UA or non-ACS, with consequences for costs and outcome There is a small survival benefit (RR 1.01) of treating early compared with treating late (presentation testing *vs.* standard testing)	10 hours' Tn testing has perfect sensitivity and specificity (as it is the reference standard) Presentation blood tests taken in ED and results available and decision made within 2 hours of sampling For testing at 10–12 hours delays according to scenario used

continued

TABLE 9 Summary of included full papers (*continued*)

Study details	Goodacre *et al.*[78] and Fitzgerald *et al.*[79]	Vaidya *et al.*[81]	Thokala *et al.*[80] and Goodacre *et al.*[7]	CADTH report[82]	Collinson *et al.*[19]
Perspective	NHS	Health care	NHS	Publicly funded health care system	NHS in England and Wales
Discount rate	Not mentioned	No information	Nothing mentioned	5% discount rate applied to costs and QALYs	Nothing mentioned
Uncertainty around cost-effectiveness ratio expressed	ICE plane, probability of strategy being dominated/ cost-effective	CEACs (not shown in abstract)	CEACs for PSA results, per scenario	As reported in outcomes of one-way sensitivity analyses, and also (for PSA) in CEACs	CEACs
Sensitivity analysis	PSA	One way and probabilistic	One-way sensitivity analyses, scenario analyses (doctor on demand, twice-daily ward round, and once-daily ward round), and PSA		Secondary analysis using cTnI instead of cTnT, scenario analysis (doctor on demand, once-daily ward round, twice-daily ward round) and PSA
Outcome (cost and LYs/QALYs) per comparator	*Empirical 3 months*: point of care £1217, QALY 0.158 SC £1006, QALY 0.161 For the model, no outcomes per comparator were reported	No information	For doctor-on-demand scenario, per 1000 patients without known CAD: No testing £965,994 QALY 26,227 Presentation standard Tn, 10% CV £1,560,361 QALY 26,345 Presentation standard Tn, 99th percentile £1,609,760 QALY 26,352 Presentation hs-trop, 99th percentile £1,806,910 QALY 26,279 10 hours Tn £2,016,540 QALY 26,286	cTnI US$2,018 QALY 8.1385 hs-cTnI US$2,082 QALY 3.1389 hs-cTnT US$2,186 QALY 8.1399	For doctor-on-demand scenario, per 1000 patients: No testing £965,994 QALY 26,227 hs-cTnT at presentation £1,581,263 QALY 26,349 hs-cTnT at presentation and 90 min £1,715,526 QALY 26,354 hs-cTnT and H-FABP at presentation £1,682,362 QALY 26,359 10-hour Tn £2,016,540 QALY 26,386

Study details	Goodacre *et al.*[78] and Fitzgerald *et al.*[79]	Vaidya *et al.*[81]	Thokala *et al.*[80] and Goodacre *et al.*[7]	CADTH report[82]	Collinson *et al.*[19]
Summary of incremental analysis	*Empirical 3 months*: Increment point of care vs. SC £211 QALY –0.00282 Probability point of care cost-effective at £20,000/QALY = 0.4% *Decision model 3 months*: Increment point of care vs. SC £169 QALY –0.002 Probability point of care cost-effective at £20,000/QALY = 22.3% *Decision model lifetime*: Increment point of care vs. SC £329 QALY –0.087 Probability point of care cost-effective at £20,000/QALY = 33.6%	hsTnT vs. cTnT: incremental €111 and 16–17 lives per 1000 AMI ICER 3748 €/QALY hsTnT + H-FABP vs. cTnT: incremental €178 ICER 5717 €/QALY	For doctor-on-demand scenario: Presentation standard Tn 10% CV vs. no testing: £5030/QALY Presentation standard Tn 99th percentile vs. presentation standard Tn 10% CV: £6518/QALY Presentation hs-Tn 99th percentile vs. presentation standard Tn 99th percentile: £7487/QALY 10 hours' Tn vs. presentation hs-Tn 99th percentile: £27,546/QALY	cTnI reference hs-cTnI incremental costs US$64, incremental QALYs 0.000352 dominated (by extension) hs-cTnT incremental costs US$168, incremental QALYs 0.001408 ICER US$119,377/QALY	No testing – reference strategy hs-cTnT compared with no testing ICER £5012/QALY hs-cTnT at presentation and at 90 minutes: dominated hs-cTnT and H-FABP compared with hs-cTnT at presentation: ICER £11,026/QALY (as reported but the correct number should be 10,871) 10-hour Tn compared with Hs-cTnT and H-FABP: ICER £12,090/QALY Conclusion: if a rapid-rule out strategy with a sensitivity of 95% (and specificity of around 90%) would be available, then a 10-hour Tn strategy does not seem cost-effective

CEAC, cost-effectiveness acceptability curve; ICE, incremental cost-effectiveness; MI, myocardial infarction; PSA, probabilistic sensitivity analysis; PSSRU, Personal Social Services Research Unit; RATPAC, Randomised Assessment of Treatment using Panel Assay of Cardiac Markers.

TABLE 10 Checklist of study quality for full papers included

	Goodacre *et al.*[78] and Fitzgerald *et al.*[79]	Vaidya *et al.*[81]	Thokala *et al.*[80] and Goodacre *et al.*[7]	CADTH report[82]	Collinson *et al.*[19]
Study design					
The research question is stated	✓	✓	✓	✓	✓
The economic importance of the research question is stated	✓	✗	✓	✓	✓
The viewpoint(s) of the analysis are clearly stated and justified	✓	✓	✓	✓	✓
The rationale for choosing alternative programmes or interventions compared is stated	✓	✗	✓	✓	✓
The alternatives being compared are clearly described	✓	✓	✓	✓	✓
The form of economic evaluation used is stated	✓	✓	✓	✓	✓
The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓	✓	✓	✓
Data collection					
The source(s) of effectiveness estimates used are stated	✓	✗	✓	✓	✓
Details of the design and results of effectiveness study are given (if based on a single study)	✓	✗	✓	✓	✓
Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	✓	✗	✓	✓	✓
The primary outcome measure(s) for the economic evaluation are clearly stated	✓	✓	✓	✓	✓
Methods to value benefits are stated	✓	✗	✓	✓	✗
Details of the subjects from whom valuations were obtained were given	✓	✗	✗	✗	✗
Productivity changes (if included) are reported separately	NA	✗	NA	NA	NA
The relevance of productivity changes to the study question is discussed	NA	✗	NA	NA	NA
Quantities of resource use are reported separately from their unit costs	✓	✗	✗	✗	✗
Methods for the estimation of quantities and unit costs are described	✓	✗	✓	✓	✓
Currency and price data are recorded	✓	✗	✓	✓	✓

TABLE 10 Checklist of study quality for full papers included (*continued*)

	Goodacre *et al.*[78] and Fitzgerald *et al.*[79]	Vaidya *et al.*[81]	Thokala *et al.*[80] and Goodacre *et al.*[7]	CADTH report[82]	Collinson *et al.*[19]
Details of currency of price adjustments for inflation or currency conversion are given	✓	✗	✗	✗	✗
Details of any model used are given	✓	✗	✓	✓	✓
The choice of model used and the key parameters on which it is based are justified	✓	✗	✓	✓	✓
Analysis and interpretation of results					
Time horizon of costs and benefits is stated	✓	✓	✓	✓	✓
The discount rate(s) is stated	✗	✗	✗	✓	✗
The choice of discount rate(s) is justified	NA	✗	NA	✓	NA
An explanation is given if costs and benefits are not discounted	✗	✗	✗	NA	✗
Details of statistical tests and CIs are given for stochastic data	✓	✗	✓	✓	✓
The approach to sensitivity analysis is given	✓	✗	✓	✓	✓
The choice of variables for sensitivity analysis is justified	✓	✗	✓	✓	✓
The ranges over which the variables are varied are justified	✓	✗	✓	✓	✓
Relevant alternatives are compared	✓	✓	✓	✓	✓
Incremental analysis is reported	✓	✗	✓	✓	✓
Major outcomes are presented in a disaggregated as well as aggregated form	✓	✗	✓	✓	✓
The answer to the study question is given	✓	✓	✓	✓	✓
Conclusions follow from the data reported	✓	✓	✓	✓	✓
Conclusions are accompanied by the appropriate caveats	✓	✗	✓	✓	✓

NA, not applicable.

Goodacre (2011)[78] and Fitzgerald (2011)[79]

This study was based on the multicentre, pragmatic controlled trial 'Randomised Assessment of Treatment using Panel Assay of Cardiac Markers' (RATPAC). An economic evaluation was undertaken to assess the cost-effectiveness of management based on testing with a panel of point-of-care cardiac markers compared with management without point-of-care panel assessment. The included population consisted of patients presenting to hospital with chest pain attributable to suspected, but not proven, AMI and no other potentially serious alternative pathology or comorbidity. The analysis was performed from an NHS perspective, using trial data to estimate the mean costs per patient of chest pain-related care and the mean number of QALYs accrued by patients in each arm of the trial, with a time horizon of 3 months. In addition, a decision-analytic model was constructed to duplicate (validate) trial results and extrapolate results to a longer time horizon.

Resource-use data were collected for all patients. Cost and outcome data were collected using patient notes and self-completed questionnaires. Unit prices were based partly on a microcosting study on a sample of patients, partly on a study previously undertaken by the investigators, and partly on purchase price and national unit costs. QALYs were calculated based on European Quality of Life-5 Dimensions (EQ-5D) measurements. In a sensitivity analysis, productivity costs were included as reported by the patients.

As it was anticipated that the trial would have limited power to detect a difference in major adverse events, the decision-analytic model was intended to explore whether uncertainty around the effect of the intervention upon the major adverse event rate could influence the potential cost-effectiveness of the intervention. The model used trial data to estimate costs and QALYs up to 3 months. Beyond this, lifetime cost and QALYs were estimated from a previous study.[86] It was assumed that patients who had died at 3 months would accrue no further costs or QALYs. Those who had survived non-fatal myocardial infarction (MI) would accrue costs and QALYs associated with CHD (estimated at £10,079 and 6.829, respectively). Those without CHD were assigned zero costs and 20 QALYs.

Empirical results showed that the point-of-care test strategy was dominated by standard care, which delivered slightly more QALYs at a lower cost. The probability that point-of-care testing would be more cost-effective than standard care at a willingness-to-pay threshold of £20,000 per QALY was < 1%. The decision-analytic model again resulted in higher costs and less effect for the point-of-care panel assay compared with standard care, also when extrapolated to lifetime survival. The probability of the point-of-care panel assay being cost-effective for the 3-month and lifetime model was 22.3% and 33.6%, respectively.

The main conclusion was that point-of-care panel assay testing is unlikely to be considered cost-effective in the NHS, with an 89% probability that standard care was dominant. Cost-effectiveness was mainly driven by differences in mean cost, with point estimates suggesting that, per patient, point-of-care panel assessment was £211 more expensive than standard care.

Vaidya (2012)[81]

This study aimed to assess the cost-effectiveness of a hs-TnT assay, alone or in combination with the H-FABP assay in comparison with the conventional cTnT assay for the diagnosis of AMI in patients presenting to hospital with chest pain. A decision-analytic model was developed to perform both a cost–utility analysis (cost per QALY gained) and a cost-effectiveness analysis [cost per life-year (LY) gained and cost per AMI averted], using a health-care perspective and a lifetime time horizon. One-way and probabilistic sensitivity analyses (PSAs) were conducted.

The incremental cost-effectiveness ratio (ICER) for hs-TnT compared with conventional cTnT was €3748 per QALY gained. For hs-cTnT in combination with H-FABP compared with conventional cTnT the ICER was €5717 per QALY gained. For LY and AMI averted, no ICERs were reported in the abstract. The PSA showed the hs-TnT assay to be the preferable strategy, with a probability of > 90%, at a ceiling ratio of €4800 per QALY. This led to the conclusion that the hs-TnT assay is very cost-effective relative to the conventional cTnT assay. Combining hs-TnT with H-FABP did not seem to offer any additional economic or health benefit over the hs-TnT test alone.

Goodacre (2013)[7] and Thokala (2012)[80]

This study aimed to estimate the cost-effectiveness of using alternative biomarker strategies to diagnose MI, and using biomarkers, computed tomography coronary angiography (CTCA) and exercise ECG to risk-stratify Tn-negative patients. As the second aim was outside the scope of this review, we have summarised only the analysis that compares the biomarker strategies for diagnosing MI, referred to in the HTA report as 'the diagnostic phase model'. The different diagnostic strategies were applied to a hypothetical cohort of patients attending the ED with suspected, but not proven, ACS. Patient characteristics were defined using data from the RATPAC trial,[87] as well as patients' arrival times during the day at the ED. The model assigned each patient a probability of re-infarction or death depending on their characteristics and whether or not they had treatment. The model took a lifetime time horizon. The economic perspective was that of the NHS in England and Wales.

The following strategies were applied to each patient:

- no testing – discharge all patients without treatment (hypothetical)
- standard Tn assay measured at presentation using the 10% CV as the threshold for positivity
- standard Tn assay measured at presentation using the 99th percentile threshold
- high-sensitivity Tn assay measured at presentation using the 99th percentile threshold
- standard Tn assay measured at presentation and 10 hours after symptom onset using the 99th percentile threshold.

Blood tests at presentation were assumed to be taken in the ED, and so a decision could be made within 1 hour of the test results becoming available. For the 10–12 hours' Tn measurement, three different scenarios were tested:

- 'doctor-on-demand' scenario, with medical staff available 24 hours a day to make a disposition decision within 1 hour of the results being available
- twice-daily ward round scenario, with medical staff only available at twice daily ward rounds to make disposition decisions
- once-daily ward round scenario, with medical staff only available at a once daily ward round to make disposition decisions.

Sensitivity and specificity estimates for the presentation Tn tests were obtained by performing meta-analysis of estimates from individual primary studies included in the accompanying review. The 10-hour Tn test was assumed to have perfect sensitivity and specificity as it was the reference standard for the review. This implies that FPs of the hs-Tn testing at presentation will still be discharged home after the 10- to 12-hour Tn test but FNs will be discharged home without treatment. The 'discharge without testing or treatment' by definition has perfect specificity, but a sensitivity of 0%.

The risk of re-infarction and death for patients with MI was based on a study by Mills *et al.*[83] Life expectancy of patients with MI, and MI with re-infarction, was estimated from Polanczyk *et al.*,[88] whereas the utility of patients with MI was based on Ward *et al.*[85] The utility of patients with re-infarction was estimated by using a multiplicative factor of 0.8 for patients with MI (expert opinion). Patients without MI were assigned the life expectancy and utility scores of the general population. Lifetime costs for patients with MI were based on Ward *et al.*[85] One-way sensitivity analyses were performed, as well as a PSA. In a secondary analysis, a strategy was added that involved alternative biomarkers in combination with the presentation Tn testing.

The results showed that measuring a 10-hour Tn level in all patients was the most effective strategy (ICER £27,546–103,560). However, at a threshold of £30,000 per QALY, the optimal strategy in all but one scenario was measurement of high-sensitivity Tn at presentation, with a 10-hour Tn test if positive and discharge home if negative (ICER £7487–17,191 per QALY). The exception was a scenario involving patients without known CAD and a doctor available on demand to discharge the patient, where, using the £30,000 per QALY threshold, the strategy of measuring a 10-hour Tn level in all patients was optimal

(ICER of £27,546 per QALY). Sensitivity analyses showed the optimal strategy to vary with different levels of sensitivity and timing of the tests.

The report concluded that the additional costs that are likely to be incurred by measuring a 10-hour Tn level, compared with a presentation high-sensitivity Tn level, are unlikely to represent a cost-effective use of NHS resources in most of the scenarios tested.

Canadian Agency for Drugs and Technologies in Health optimal use report

This report[82] aimed to determine the cost-effectiveness of hs-cTnT and hs-cTnI assays compared with each other, as well as with cTnI assays in patients with suspected ACS symptoms in the ED. For this purpose, three comparators were considered: hs-cTnT, hs-cTnI and cTnI. As cTnT is no longer available in Canada, it was not taken into account in the analysis. The target population consisted of 65-year-old patients presenting to the ED, without ST segment elevation, who required cTn testing for diagnosis of NSTEMI. For the economic evaluation, a decision tree was constructed, which calculated lifetime cost per QALY from the perspective of a publicly funded health-care system.

The model consisted of a short-term part, which had a time horizon of 1 year, and a long-term part. The short-term part incorporated the testing and treatment procedures and short-term outcomes. Patients were tested at presentation at the ED and, if they were not admitted to hospital after the first test, they were tested again after 6 hours. When the patient was admitted after the first test, treatment was said to be initiated early, and when a patient was admitted after the second test, treatment was late. One-year mortality depended on whether a patient had NSTEMI and whether they were treated early, treated late, or untreated (in the case of FN test results). Those not suffering from NSTEMI were further stratified into UA or not having ACS (non-ACS). The annual probability of death in the long-term part of the model was dependent on patient age, sex, and whether or not they had suffered a NSTEMI, UA or did not have any type of ACS in the short-term part of the model.

The sensitivity and specificity for each cTn test at presentation to the ED was derived from the systematic review which was also part of this study. In the model, patients with a negative cTn test at presentation were assumed to be observed and have a second cTn test 6 hours later. After the second cTn test, 90% of these FNs were assumed to become TPs.

Short-term mortality rates and relative risks (RRs) for treated/non-treated were taken from published clinical studies and one non-referenced study. The RR for late treatment compared with early treatment was derived from expert opinion. Long-term mortality rates were taken from published clinical studies, and one non-referenced study. QALYs were calculated by incorporating an age-specific utility decrement for patients with NSTEMI. A number of one-way sensitivity analyses were performed, as well as a PSA.

The base-case results indicated that hs-cTnI was dominated by hs-cTnT, when compared with cTnI, at an ICER of US$119,377 per QALY. The PSA showed that, for willingness-to-pay thresholds of up to US$124,000, cTnI had the highest probability of being cost-effective. For thresholds > US$124,000, hs-cTnT had the highest probability of being cost-effective. The hs-cTnI test was not likely to be cost-effective for any value of the threshold.

The authors concluded that hs-cTnT would be considered the most cost-effective testing strategy if willingness to pay for a QALY is US$119,377 or more, otherwise cTnI would be the most cost-effective test. However, there was a lot of uncertainty in results when model assumptions were changed.

Collinson (2013)[19]

This study used the decision tree developed in the related HTA by Goodacre *et al.*[7] to compare the cost-effectiveness of five diagnostic strategies to a hypothetical cohort of patients presenting to hospital with symptoms suggestive of MI but with no diagnostic ECG changes, no known history of CHD and no major comorbidities requiring inpatient treatment. Essentially, this was a substudy of the point-of-care arm

of the RATPAC trial. All methods and model inputs were identical to the study by Thokala *et al.*[80] and the HTA report by Goodacre *et al.*,[7] but with slightly different strategies applied to the cohort of patients:

- No testing – discharge all patients without treatment (theoretical 'zero' option)
- high-sensitivity cTnT at presentation – discharge home if test is negative or admit to hospital for Tn-testing at 10–12 hours if positive
- high-sensitivity cTnT and H-FABP at presentation – discharge home if both tests are negative or admit to hospital for Tn testing at 10–12 hours if either test is positive
- high-sensitivity cTnT at presentation and at 90 minutes as in the RATPAC protocol – discharge home if both tests are negative or admit to hospital testing at 10–12 hours if either test is positive
- standard Tn testing at 10–12 hours (current standard as per NICE guidelines).

The difference with the other studies is in the addition of H-FABP in the third strategy and in the second high-sensitive Tn test at 90 minutes in the fourth strategy. In a secondary analysis, cTnT was replaced by cTnI. Sensitivity and specificity of presentation biochemical testing were estimated using data from within the study (RATPAC). Standard Tn testing at 10–12 hours was assumed to have perfect sensitivity and specificity as this was again the reference standard.

At the £20,000 per QALY threshold, 10-hour Tn testing was cost-effective (£12,090 per QALY) in the doctor-on-demand scenario, but not in the other scenarios (once-daily ward round and twice-daily ward rounds), when high-sensitivity cTnT and H-FABP measurement at presentation was cost-effective. At the £30,000 per QALY threshold, 10-hour Tn testing was cost-effective in the doctor-on-demand scenario and twice-daily ward rounds scenario (£24,600 per QALY), whereas the TnT and H-FABP measurement at presentation strategy was cost-effective (£14,806 per QALY) in the once-daily ward round scenario. Secondary analysis using cTnI instead of cTnT showed that cTnI testing at presentation and at 90 minutes was cost-effective in all three scenarios at the £20,000 per QALY threshold, and in two of the scenarios at the £30,000 per QALY threshold, with 10-hour Tn being cost-effective only in the doctor-on-demand scenario (£24,327 per QALY). The overall conclusion was that 10-hour Tn testing is likely to be cost-effective compared with rapid rule-out strategies only if patients can be discharged as soon as a negative result is available and a £30,000 per QALY threshold is used.

Summary of studies included in the cost-effectiveness review

Most of the studies identified in this review have found that the question of whether hs-Tn testing is cost-effective cannot be answered unequivocally. In favour of hs-Tn testing, the abstract by Vaidya *et al.*[81] concluded that hsTnT testing is 'very cost-effective' and the study by Goodacre *et al.*[7] concluded that 'the optimal strategy in all but one scenario was high-sensitivity Tn at presentation, with a 10 hour Tn test if positive and discharge home if negative' (p. xv). The other papers reported ICERs that were considerably higher and with substantial uncertainty. The accuracy of high-sensitivity tests and the efficiency of decision-making based on test results were important drivers of cost-effectiveness.

Model structure and methodology

Troponin tests considered in the model

The health-economic analysis will estimate the cost-effectiveness of different Tn testing methods for diagnosing or ruling out NSTEMI, in patients presenting at the ED with suspected NSTE-ACS, who have no major comorbidities requiring hospitalisation (e.g. as HF or arrhythmia) and in whom STEMI has been ruled out. Those diagnosed with NSTEMI will then be admitted to the hospital for AMI treatment and those diagnosed as without NSTEMI can be discharged without AMI treatment and further hospital stay. AMI treatment might include aspirin, statins and ACE inhibitors and consideration of coronary revascularisation for high-risk cases.[7] Initiating AMI treatment for NSTEMI will reduce the probability of MACEs, particularly cardiac death and re-infarction.

Standard serial Tn testing, for patients with acute chest pain attributable to possible ACS, does not achieve optimal sensitivity in detecting AMI until 10–12 hours after onset of symptoms. Waiting for 10–12 hours after symptom onset is burdensome for patients and induces additional health-care costs. Therefore, various alternatives have been proposed, using more sensitive Tn tests, for the early rule-out of NSTEMI (within the 4-hour NHS ED target).[89]

Two hs-cTn assays (Roche Elecsys hs-cTnT and Abbott ARCHITECT hs-cTnI) are currently used in NHS laboratories in England and Wales. One additional assay (Beckman Coulter hs-cTnI) was listed in the scope for this assessment, pending CE marking. However, each of these tests can be used at different time points and with different diagnostic thresholds, resulting in multiple possible strategies for each test. Whether or not a test strategy was included in the economic model was decided based on optimal diagnostic performance, given the available evidence on accuracy for a population with STEMI ruled out, and on applicability in clinical practice (see *Results of the assessment of clinical effectiveness assessment*, above). The test strategies evaluated in the model are:

- Standard Tn at presentation and at 10–12 hours (reference standard).
- Roche Elecsys hs-cTnT at presentation: 99th centile threshold.
- Roche Elecsys hs-cTnT (optimal strategy): LoB threshold at presentation followed by 99th centile threshold peak within 3 hours and/or Δ20% (compared with presentation test) at 1–3 hours (see *Figure 9*).
- Abbott ARCHITECT hs-cTnI at presentation: 99th centile threshold.
- Abbott ARCHITECT hs-cTnI (optimal strategy): LoD threshold at presentation, followed by 99th centile threshold at 3 hours (see *Figure 11*).
- Beckman Coulter hs-cTnI at presentation: 99th centile threshold.
- No testing, discharge all patients without testing or treatment (only in sensitivity analyses). A Tn test may not be indicated when clinical judgement assesses the probability that a patient is experiencing an AMI as low. Therefore, consistent with the protocol, this hypothetical strategy is included in sensitivity analyses wherein the AMI prevalence is varied.

In the base case, it was assumed that standard Tn had perfect sensitivity and specificity (reference case) for diagnosing AMI. Using this assumption, all patients testing positive on a hs-cTn test but negative on the standard Tn would be classified as FPs. This implies that their risk for adverse events would be the same as for those patients testing negative on both the hs-cTn test and the standard Tn, and that they ought to be discharged home without further immediate treatment. However, recent evidence has shown that patients with a negative standard Tn, but a positive hs-cTn, may be at higher risk for adverse events than patients who test negative on both the standard and the high-sensitive Tn (Goodacre S, Medstar Washington Hospital Center, Washington, DC, USA; Lipinski M, University of Sheffield, Sheffield, UK: 2014, personal communication). A secondary analysis was therefore performed, which attributed a higher risk of adverse events to a proportion of patients testing FP with the hs-cTn test.

Based on the available evidence, two analyses were performed:

- Base-case analysis.
- Secondary analysis, assuming that FPs in the hs-cTn testing strategies do not have the same risk for adverse events as TNs. Instead, these patients were assigned a higher risk for (re-)infarction and death, to reflect the idea that when the hs-cTn test gives a positive result, in some cases this must be caused by a disease process, whether or not the strict definition of AMI is met. The risk of adverse events in patients with positive hs-cTn but a negative standard Tn is higher than the patients testing negative on both the hs-cTn test and the standard Tn, but lower than risk of adverse events in patients diagnosed with NSTEMI (i.e. both positive hs-cTn and standard Tn).

Model structure

This assessment uses the HTA report by Goodacre *et al.*[7] as a starting point for cost-effectiveness modelling. The Goodacre report compared the cost-effectiveness of several diagnostic strategies for ACS. The assessment group received the health-economic model (in SIMUL8 2011, Simul8 Corporation, Boston, MA, USA) that this HTA was based on, and this model was used as a starting point to develop a de novo model (in Microsoft Excel 2003: Microsoft Corporation, Redmond, WA, USA) adapted to better fit the scope of the current assessment. In the health-economic model the mean expected costs and QALYs were calculated for each alternative strategy. These long-term consequences were estimated based on the accuracy of the different testing strategies followed by AMI treatment or discharge from the hospital without AMI treatment for patients presenting at the ED with suspected NSTE-ACS, including patients with NSTEMI and patients without NSTEMI, who are further subdivided into 'No ACS, no UA' and 'Unstable angina'. For this purpose a decision tree and a Markov model were developed. The decision tree was used to model the 30-day outcomes after presentation, based on test results and the accompanying treatment decision. These outcomes consisted of 'No ACS, no UA', 'Unstable angina', 'Non-fatal AMI (untreated)', 'Non-fatal AMI (treated)' and 'Death'. The decision tree is shown in *Figure 14*.

The long-term consequences in terms of costs and QALYs were estimated using a Markov cohort model (*Figure 15*) with a lifetime time horizon (60 years). The cycle time was 1 year, except for the first cycle,

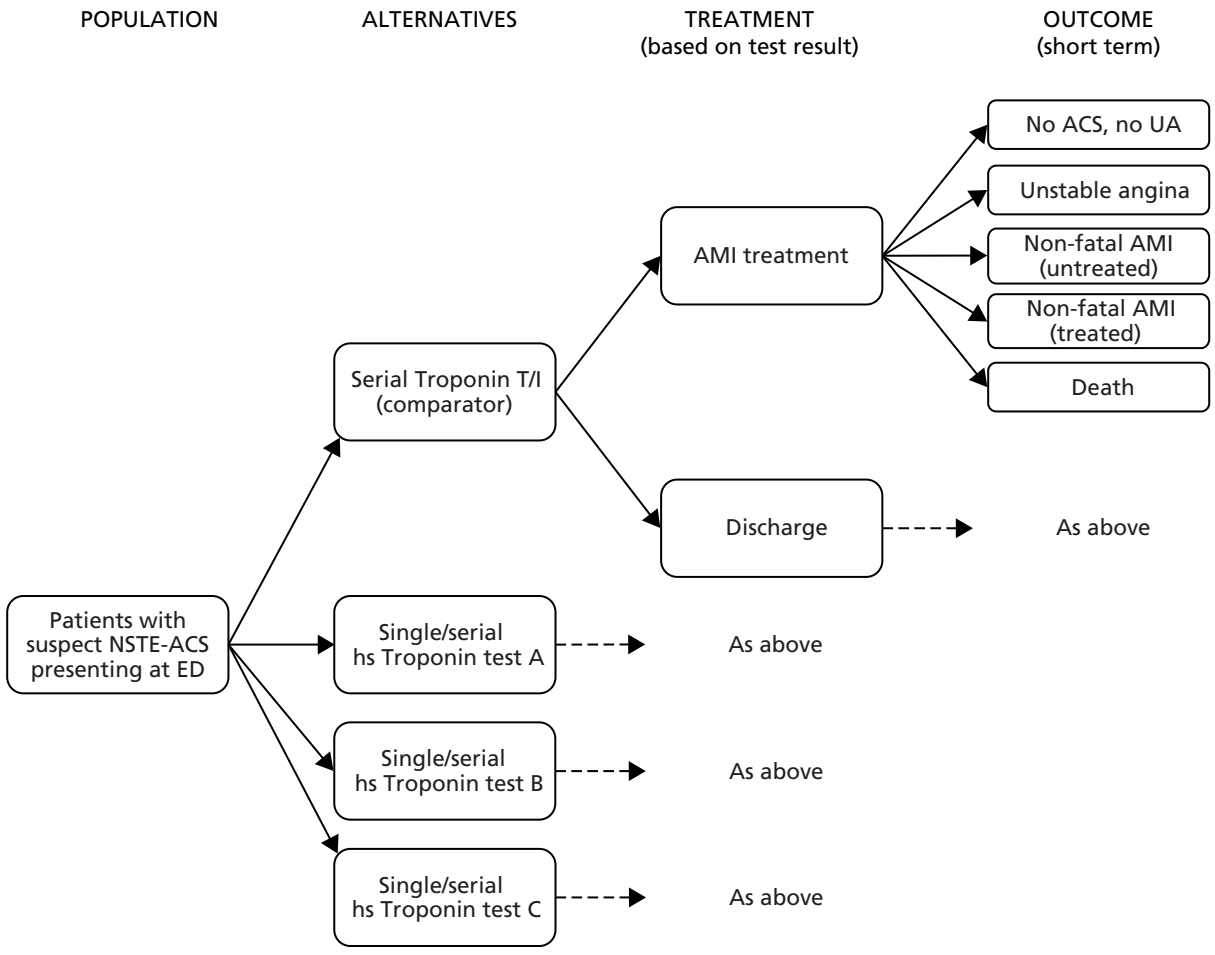

FIGURE 14 Decision tree structure.

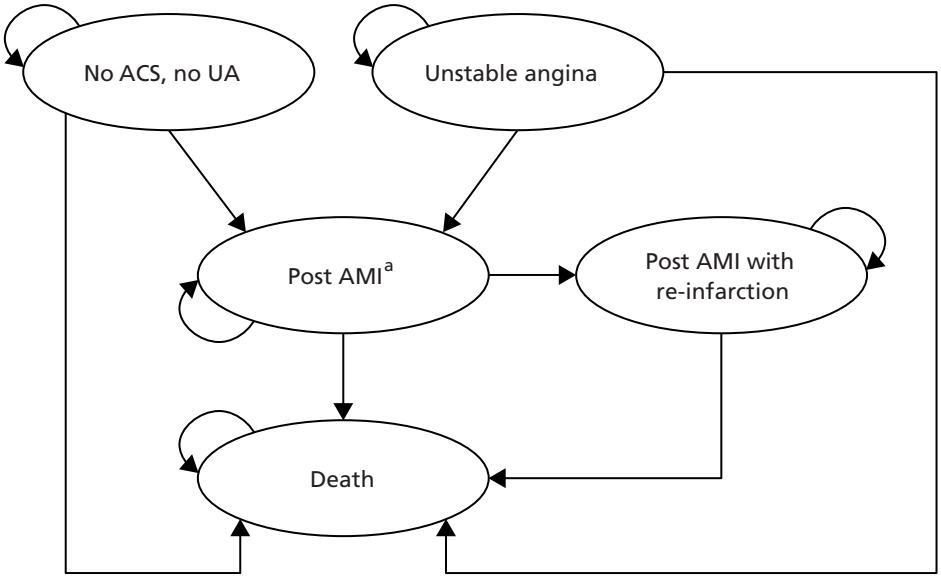

FIGURE 15 Markov model structure. a, During the first year post AMI, a distinction is made between treated and untreated AMI.

which was adjusted to 335.25 days (365.25–30) to ensure that the decision tree period (30 days) and the first cycle combined summed to 1 year. The following health states were included:

- 'No acute coronary syndrome and no unstable angina (no ACS, no UA)'
- 'Unstable angina'
- 'Post AMI (treated and untreated)'
- 'Post AMI with re-infarction'
- 'Death'.

Model parameters

Estimates for the model input parameters were retrieved from the literature and by consulting experts for unpublished data. Accuracy estimates were derived from the systematic review component of this assessment (see *Results of the assessment of clinical effectiveness assessment,* above).

Transition probabilities

An overview of transition probabilities is provided in *Table 11*.

Decision tree

The proportions of patients testing positive or negative (and thus commencing AMI treatment or being discharged from the hospital) were based on the estimated accuracy of the testing strategies considered (*Table 12*) and the estimated prevalence of NSTEMI in the UK [17.0% with standard error (SE) 2.8%; see *Table 11*].[39,40,46,64] This prevalence was higher than that derived from the RATPAC trial[78] and used in the Goodacre model,[7] because the RATPAC study population was a low-risk population.[79,87] The proportion of TPs, FPs, FNs and TNs were calculated as follows:

- TP = NSTEMI prevalence × sensitivity
- FP = (1 – NSTEMI prevalence) × (1 – specificity)
- FN = NSTEMI prevalence × (1 – sensitivity)
- TN = (1 – NSTEMI prevalence) × specificity.

Subsequently, the proportions of patients who receive AMI treatment (TP + FP), and who are discharged without AMI treatment (TN + FN) were calculated. These results are listed in *Table 13*.

TABLE 11 Transition probabilities

Parameter	Estimate	SE/95% CI	Distribution	Source
Decision tree (short term)				
NSTEMI prevalence[a]	0.170	0.028	Beta	Santalo (2013),[40] Aldous (2012),[46] Sebbane (2013),[64] APACE[39]
Proportion of UA (of all non-NSTEMI patients)	0.160	0.038	Beta	CADTH (2013)[82]
Decision tree (30 day) probabilities				
Mortality (30 day) treated AMI	0.097	0.012	Beta	Pope (2000)[90]
Mortality (30 day) untreated AMI	0.105	0.069	Beta	Pope (2000)[90]
Mortality (30 day) treated UA	0.021	0.005	Beta	Pope (2000)[90]
Mortality (30 day) no ACS	[b]	–	Fixed	ONS[91]
Markov model (long term)				
AMI incidence	[c]	–	Fixed	British Heart Foundation[92]
Annual re-infarction (treated)[d]	0.023	0.001	Beta	Smolina (2012)[93]
RR re-infarction (untreated vs. treated)[e]	2.568	1.366 to 5.604	Log-normal	Mills (2011)[83]
Annual mortality no ACS	[b]	–	Fixed	ONS[91]
Annual mortality post MI[d]	0.066	0.000	Beta	Smolina (2012)[93]
Annual mortality post re-infarction[d]	0.142	0.002	Beta	Smolina (2012)[93]
HR mortality (UA vs. NSTEMI)	0.781	0.581 to 1.053	Log-normal	Allen (2006)[94]
RR mortality (untreated vs. treated)[d]	1.877	0.951 to 4.239	Log-normal	Mills (2011)[83]
Secondary analysis (adjusted RR for patients tested FP)				
OR AMI[f]	0.840	0.578–1.235	Log-normal	Goodacre S, Lipinski M, personal communication; Lipinski *et al.*[95]
OR death[f]	0.649	0.465–0.901	Log-normal	Goodacre S, Lipinski M, personal communication; Lipinski *et al.*[95]
Proportion of AMI[g]	0.105	0.011	Beta	Goodacre S, Lipinski M, personal communication; Lipinski *et al.*[95]
Proportion of death[g]	0.114	0.011	Beta	Goodacre S, Lipinski M, personal communication; Lipinski *et al.*[95]
RR AMI[f,h]	0.855	0.602–1.197	Log-normal	Goodacre S, Lipinski M, personal communication; Lipinski *et al.*[95]
RR death[f,h]	0.676	0.500–0.911	Log-normal	Goodacre S, Lipinski M, personal communication; Lipinski *et al.*[95]

HR, hazard ratio; OR, odds ratio; SE, standard error.

a Prevalence was used to calculate the proportions of TPs/FPs and TNs/FNs based on test accuracy. Prevalence was calculated using identified studies that included NSTEMI data (see *Multiple samples*, above).

b Based on age-dependent mortality from the general population.

c Age-dependent incidence from the general population.

d Weighted average based on sex (58.1% males[7]).

e Increased re-infarction and mortality risk for untreated (vs. treated) was assumed for the first year after presentation at ED, after which no increased risk was assumed (RR = 1.0).

f For patients with both positive high-sensitivity and standard Tn tests vs. patients with positive high-sensitivity and negative standard Tn tests.

g Proportion for patients with both positive high-sensitivity and standard Tn tests. This proportion is only used to covert ORs to RRs.

h ORs were converted to RRs using the method described by Zhang and Yu.[96]

TABLE 12 Test accuracy

Strategy	Sensitivity (SE)[a]	Specificity (SE)[a]	Distribution	Source
Serial standard Tn testing	1.00 (–)	1.00 (–)	Fixed	Assumption
Roche Elecsys hs-cTnT (99th centile at presentation)	0.88 (0.04)	0.84 (0.04)	Multivariate normal	*Chapter 3*
Roche Elecsys hs-cTnT (optimal strategy)[b]	0.93 (0.02)[c]	0.82 (0.01)[c]	Multivariate normal	*Chapter 3*
Abbott ARCHITECT hs-cTnI (99th centile at presentation)	0.80 (0.02)	0.93 (0.00)	Multivariate normal	*Chapter 3*
Abbott ARCHITECT hs-cTnI (optimal strategy)[d]	0.98 (0.01)[c]	0.94 (0.01)[c]	Multivariate normal	*Chapter 3*
Beckman Coulter hs-cTnI (99th centile)	0.92 (0.02)	0.75 (0.01)	Multivariate normal	*Chapter 3*
No Tn test[e]	0.00 (–)	1.00 (–)	Fixed	Assumption

a Correlation between sensitivity and specificity was calculated to be –0.262 based on the covariance matrix from the *metandi* output for the Roche Elecsys hs-cTnT (99th centile at presentation) test (see also *Chapter 3*). This correlation was assumed to be equal for other tests as it was not possible to obtain the covariance matrix for the other tests included in the economic analyses (a minimum of four studies is required).
b Calculated based on accuracy data for the Roche Elecsys hs-cTnT optimal testing strategy.
c Standard error based on PSA.
d Calculated based on accuracy data for the Abbott ARCHITECT optimal testing strategy.
e The no-testing strategy is considered only in sensitivity analyses.

TABLE 13 Test outcomes

Strategy	TP	FP	FN	TN	PPV	NPV	LR+	LR–
Serial standard Tn testing	0.17	0.00	0.00	0.83	1.00	1.00	1.00	0.00
Roche Elecsys hs-cTnT (99th centile at presentation)	0.15	0.13	0.02	0.70	0.53	0.97	5.41	0.15
Roche Elecsys hs-cTnT (optimal strategy)	0.16	0.15	0.01	0.68	0.51	0.98	5.05	0.09
Abbott ARCHITECT hs-cTnI (99th centile at presentation)	0.14	0.06	0.03	0.77	0.70	0.96	11.47	0.21
Abbott ARCHITECT hs-cTnI (optimal strategy)	0.17	0.05	0.00	0.78	0.76	1.00	15.67	0.02
Beckman Coulter hs-cTnI (99th centile)	0.16	0.21	0.01	0.62	0.43	0.98	3.67	0.11
No Tn test[a]	0.00	0.00	0.17	0.83	0.00	0.83	0.00	1.00

PPV, positive predictive value.
a The no-testing strategy is considered only in sensitivity analyses; the FN rate represents the prevalence of NSTEMI.

After treatment, TP patients in the decision tree were allocated to 'Non-fatal AMI (treated)' and FP patients were further subdivided between 'No ACS, no UA' and 'Unstable angina' (based on the proportion of UA among non-NSTEMI patients; see *Table 11*). After being discharged, TN patients were also subdivided between 'No ACS, no UA' and 'Unstable angina', whereas FN patients were allocated to 'Non-fatal AMI (untreated)'. The proportions of FNs, reported in *Table 13*, can be considered as the proportions of AMIs that would have been missed when assuming that standard Tn testing has perfect accuracy. Finally, to calculate the total number of deaths in the decision tree, the probability of 30-day mortality was assigned based on abovementioned subdivision (see *Table 11*). It was assumed that UA is always correctly diagnosed, hence the mortality probability for treated UA was used.

Markov model

The age-dependent AMI incidence in the UK[92] was used to model the occurrence of AMI for patients in the health states 'No ACS' and 'Unstable angina'. It was assumed that all AMIs in the Markov trace are diagnosed correctly and thus receive treatment. For patients in the 'Post-MI' health state, the probability of re-infarction after treated AMI was retrieved from a UK record linkage study ($n = 387{,}452$), which assessed long-term survival and recurrence after AMI.[93] For the current assessment the probabilities for females and males were weighted according to the estimated proportion of females and males in the population (males = 58.1%[7]). The re-infarction probability for the 'Post-MI with re-infarction' health state is equal to the re-infarction probability for the 'Post-MI' health state. The re-infarction RR for people with untreated AMI compared with treated AMI was calculated from a recent study by Mills *et al.*[83] based on patients with a Tn concentration of 5–19 ng/l. This RR was assumed only for the first year after presentation at ED, after which no increased risk was assumed (i.e. RR = 1.0 for untreated vs. treated AMI after year 1).

Age-dependent mortality from the general population was used for patients in the 'No ACS, no UA' health state.[91] For the 'Post-MI' and 'Post-MI with re-infarction' health states, mortality was extracted from the record linkage study.[93] Again, the study by Mills *et al.*[83] was used to calculate the mortality RR for untreated AMI compared with treated AMI for the first year, after which an RR of 1.0 was used. Finally, a multivariate adjusted mortality hazard ratio (HR) for UA compared with NSTEMI was retrieved from a study by Allen *et al.*[94] to calculate mortality after UA.

All input parameters for the Markov model are reported in *Table 11*.

Health-state utilities

Age-dependent utility scores, from the UK general population, were calculated for patients in the 'No ACS, no UA' health state based on a linear regression model.[85] These age-dependent utility scores from the general population were combined with age-dependent disutilities for AMI[82] to calculate utilities for the 'Post-MI' health states (with or without re-infarction). Utility scores for the 'Unstable angina' health state were calculated based on Post-MI utility scores and a utility increment of 0.010 (*Table 14*).[85]

Resource use and costs

Test-specific resource use consisted of the number of tests performed and the duration of hospital stay (hours) before discharge/AMI treatment (*Table 15*).

Health-state costs (*Table 16*) were mainly retrieved from previous economic evaluations conducted in the UK.[85,97] Health-state costs for the 'Unstable angina', 'Post-MI' and 'Post-MI with re-infarction' consisted of costs for three 15-minute general practitioner consultations and medication costs.[85] For the first year in the 'Unstable angina' health state, costs for clopidogrel (for 60%) and hospitalisation (for 50%) were added to this. The first year costs for both 'Post-MI' health states were based on resource data from the Nottingham Heart Attack Register.[97]

Additionally, costs of fatal events, retrieved from a UK economic evaluation,[85] were accumulated for all fatal AMIs. For this purpose, it was assumed that all 30-day deaths after 'true' NSTEMI were due to a fatal AMI event. In addition, AMI treatment costs were calculated based on the national tariff for

TABLE 14 Utility scores

Parameter	Estimate	SE	Distribution	Source
No ACS, no UA				
Intercept	1.060	0.029	Normal	Ward *et al.*[85]
Disutility for age	0.004	0.001	Normal	Ward *et al.*[85]
Post-MI [disutility compared with no ACS by age (years)]				
Age = 45	0.060	0.001	Normal	CADTH[82]
Age = 55	0.051	0.001	Normal	CADTH[82]
Age = 65	0.025	0.001	Normal	CADTH[82]
Age = 75	0.007	0.001	Normal	CADTH[82]
UA				
Utility increment compared with AMI	0.010	0.042	Normal	Ward *et al.*[85]

TABLE 15 Resource use (test specific)

Parameter	Estimate	SE/range	Distribution	Source
Number of tests				
Serial standard Tn testing	2.00	–	Fixed	Assumption
Roche Elecsys hs-cTnT (99th centile at presentation)	1.00	–	Fixed	Assumption
Roche Elecsys hs-cTnT (optimal strategy)	1.60	0.02	Beta[a]	*Chapter 3*
Abbott ARCHITECT hs-cTnI (99th centile at presentation)	1.00	–	Fixed	Assumption
Abbott ARCHITECT hs-cTnI (optimal strategy)	1.71	0.02	Beta[a]	*Chapter 3*
Beckman Coulter hs-cTnI (99th centile)	1.00	–	Fixed	Assumption
No Tn test[b]	0.00	–	Fixed	Assumption
Hospital stay (hours) before discharge/AMI treatment[b]				
Serial standard Tn testing	14	13–15	Beta PERT	Assumption
Roche Elecsys hs-cTnT (99th centile at presentation)	3	–	Fixed	Assumption
Roche Elecsys hs-cTnT optimal strategy (patients with AMI ruled out on first test)	3	–	Fixed	Assumption
Roche Elecsys hs-cTnT optimal strategy (patients receiving both tests)	5	4–6	–	Assumption
Abbott ARCHITECT hs-cTnI (99th centile at presentation)	3	–	Fixed	Assumption
Abbott ARCHITECT hs-cTnI optimal strategy (patients with AMI ruled out on first test)	3	–	Fixed	Assumption
Abbott ARCHITECT hs-cTnI optimal strategy (patients receiving both tests)	6	–	Fixed	Assumption
Beckman Coulter hs-cTnI (99th centile at presentation)	3	–	Fixed	Assumption
No Tn test[b]	0	–	Fixed	Assumption

a Beta distribution is used to estimate the probability of patients receiving a second test (all patients receive the presentation test).
b The no-testing strategy is considered only in sensitivity analyses.
c Includes delay from the time at which sampling could be performed to the time at which results became available (2 hours) and delay between arrival at hospital and Tn assessment commencing (1 hour).

TABLE 16 Health-state costs, event costs and unit prices

Parameter	Estimate (£)	SE/range (£)	Distribution	Source
Health-state costs				
No ACS, no UA first year	0	–	Fixed	Assumption
No ACS, no UA subsequent year	0	–	Fixed	Assumption
UA first year[a]	548	–	Fixed	Ward *et al.*[85]
UA subsequent year[a]	213	–	Fixed	Ward *et al.*[85]
Post-MI first year[a,b]	5835	488	Gamma	Palmer *et al.*[97]
Post-MI subsequent years[a,b]	213	–	Fixed	Ward *et al.*[85]
Event costs				
Costs of fatal AMI[a]	1451	–	Fixed	Ward *et al.*[85]
AMI treatment costs	3436	–	Fixed	Department of Health[98]
Unit prices				
Hospital stay costs (per hour)[c]	27	–	Fixed	Department of Health[98]
Test costs[a]	20	18–26	Beta PERT	Goodacre *et al.*,[7] Thokal *et al.*[80]

a Price inflated to the 2012–13 price level based on price indices from The Hospital and Community Health Services index.[99]
b Post MI with or without re-infarction.
c NHS reference costs were divided by 24 to obtain the hourly costs.

non-elective AMI without complications [Healthcare Resource Group (HRG) code: EB10Z].[98] To calculate the hospital stay costs for patients, based on the number of hours before the test results become available, non-elective NHS reference costs for the general medical ward were used (HRG code: EB01Z).[98] For this purpose, it was assumed that doctors were available on demand, and the time to discharge was delayed because of time between arrival at the ED and start of first sampling (1 hour) and the time between sampling and the results being available (2 hours). In the case of multiple testing, the 1-hour delay between arrival at the ED and start of sampling was applied to only the first test; however, this also affected the timing of the second test if applicable. The 2-hour delay before test results become available applies to all tests performed. Incorporating these time delays effectively implies that only tests at presentation and tests performed 1 hour after presentation could inform decisions within the NHS 4-hour ED target. All other multiple testing strategies, as well as standard Tn testing at 10–12 hours, would require a transfer from the ED to the general ward (patients are transferred to the general ward 4 hours after presentation at the ED). Finally, the test costs include panel (including reagent, machine and maintenance), calibration and quality control costs. Depending on the annual number of panels, the test costs varied between £16.18 and £21.33, for annual rates of testing of 1500 and 3000, respectively.[80] Based on clinical expert input, the average test costs were estimated to be £20 (2011 price level).[7,80]

Overview of main model assumptions

The main assumptions in the health-economic analyses were:

- Serial Tn testing (comparator) has perfect accuracy (sensitivity = 1.0 and specificity = 1.0).
- For the Roche Elecsys hs-cTnT and Abbott ARCHITECT hs-cTnI optimal strategies it was assumed that the sensitivity and specificity for the subpopulation not discharged after the presentation test is equal to the sensitivity and specificity for the initial group (presenting at the ED).
- The life expectancy, quality of life and costs for FP patients is, in the base-case analysis, equal to the life expectancy, quality of life and costs of TN patients. This assumption was amended in the secondary and sensitivity analyses.
- In contrast with AMIs occurring during the decision tree period, all AMIs (either first or re-infarction) occurring in the Markov trace are diagnosed correctly and thus treated.

- UA is always correctly diagnosed and thus treated.
- The re-infarction probability for the 'Post-MI with re-infarction' health state is equal to the re-infarction probability for the 'Post-MI' health state.
- The increased 'Post-MI' re-infarction and mortality probabilities for untreated AMI were assumed to last 1 year: afterwards a RR of 1.0 was applied (for untreated vs. treated AMI).
- There is no additional benefit of starting treatment early, so treatment effect for high-sensitive strategies is equal to treatment effect for standard Tn strategy.
- All 30-day deaths (after presentation at the ED) are due to fatal AMI events and will receive the associated costs.

Model analyses

Expected costs, LYs and QALYs were estimated for all Tn testing methods. Discount rates of 3.5% and a half-cycle correction were applied for both costs and effects. Incremental cost and QALYs for each strategy compared with standard Tn, and compared with the next best alternative, were calculated. The ICER was then calculated by dividing the incremental costs by the incremental QALYs. PSAs (10,000 simulations) were performed, and cost-effectiveness acceptability curves (CEACs) and cost-effectiveness acceptability frontiers (CEAFs) were constructed. Although CEACs can be used to illustrate decision uncertainty, the option with the highest probability of being cost-effective may not necessarily be the most cost-effective option according to the expected values. Moreover, CEAFs can be used to illustrate the decision uncertainty surrounding the most cost-effective option.[100]

Secondary analysis

For the base case, it was assumed that patients who tested negative on standard Tn and positive on hs-cTn tests would experience life expectancy and quality of life equal to TN patients. This assumption is, however, debatable, as unpublished data (Goodacre S, Lipinski M, personal communication) show that patients with a negative standard Tn test and positive hs-cTn test have an increased risk of (re-)infarction and mortality compared with those who test negative on both standard Tn and hs-cTn tests. Although this risk was not as high as in patients with both positive standard Tn and positive hs-cTn tests, it could still be considered prognostically important. Therefore, in this secondary analysis the risk of re-infarction and mortality was adjusted for patients who tested FP (see *Table 11*). It was assumed that for this proportion of patients, the relative treatment benefit would be equal to that for TP patients. As the prevalence of this 'higher risk subgroup' is likely to be the same for all comparators, it was assumed that this proportion was equal to the lowest proportion of FP patients for all hs-cTn tests (see *Table 13*). This 'higher risk subgroup' was assumed to be treated for all hs-cTn tests (as they tested positive with these tests) and untreated for the standard Tn test (as they tested negative with this test), thus affecting the probability of adverse outcomes and treatment costs. In addition, the post-MI utility and health-state costs were used for this 'higher-risk subgroup'.

Sensitivity analysis

For both the base case and the secondary analysis, the following one-way sensitivity analyses were performed to assess the impact of model assumptions and input parameters on the estimated outcomes:

Model assumptions:

- The assumption that the increased post AMI re-infarction and mortality probabilities for untreated AMI lasts for only 1 year was replaced by the assumption that these probabilities would remain elevated for a lifetime.
- The assumption that a doctor will be available on demand and thus that a decision could be made immediately (as in the base case) was replaced with an assumed delay (1, 2 or 3 hours) before a doctor is available and a decision could be made.

- As for the previous sensitivity analysis, except that the delay (1, 2 or 3 hours) applies only once patients are transferred to the general ward 4 hours after presentation (no delay in the ED).
- A total delay of 1.5 hours is assumed (includes delay from the time at which sampling could be performed to the time at which results became available and delay between arrival at hospital and Tn assessment commencing) rather than assuming a total delay of 3 hours (base case).
- AMI treatment costs are applied for patients who tested FP rather than using no treatment costs, as assumed in the base-case analysis.
- In addition to the health-state costs of UA during the first year, the AMI treatment costs are also applied for patients with UA (during the first year), rather than assuming no additional treatment costs.

Model input parameters (varied to lower and upper boundary of the 95% CI unless stated otherwise):

- test costs [test costs was varied over a wider range (£5–40) than the 95% CI]
- AMI treatment costs (±25%)
- post-MI first-year health-state costs
- utility increment for UA compared with AMI
- post-MI disutility compared with no ACS
- mortality (30 day) treated AMI (decision tree)
- mortality (30 day) untreated AMI (decision tree)
- annual re-infarction (after initial AMI)
- RR re-infarction (untreated vs. treated AMI)
- annual post-MI mortality
- annual post-MI mortality after re-infarction
- HR mortality (UA vs. NSTEMI)
- RR mortality (untreated vs. treated AMI).

Subgroup analysis

For both the base case and the secondary analysis, a number of subgroup analyses were performed. The main subgroup analyses were based on age- and sex-dependent re-infarction probabilities, mortality probabilities (for all health states), AMI incidence and quality of life, and could be applied to all test strategies. Accuracy was thus assumed to be subgroup independent (equal to the base case values). The following subgroups were identified:

- Sex.
- Age (45, 55, 65, 75 and 85 years).
- People with a history of previous NSTEMI. For this purpose, a proportion of 0% UA was assumed and the probabilities for the initial 'Post-MI' health state were used for the 'No ACS, no UA' health state and the probabilities for 'Post-MI with re-infarction' were used for the 'Post-MI' and 'Post-MI with re-infarction' health states. This subgroup analysis was performed for only the base case, as for the secondary analysis this would lead to lower mortality probabilities for FP patients than TN patients (which seems implausible).
- Subgroups with varying AMI prevalence (1%, 5%, 10%, 20%, 30%). In these analyses the no-testing strategy was included as a comparator, as a Tn test may not be indicated when clinical judgement assesses that the probability that a patient is experiencing an AMI is low. For the no-testing strategy it is assumed that patients will be discharged immediately.

It should be noted that the main subgroup analyses (described above) differ from the subgroups described in the systematic review component of this assessment (see *Chapter 3*, *Presentation samples*), for which specific accuracy and prevalence data were available. Additional subgroup analyses were performed based on these subgroup-specific accuracy data. However, these analyses could be performed for only the Roche Elecsys hs-cTnT assay at presentation sample, using the 99th centile diagnostic threshold, compared with

standard Tn testing; no subgroup-specific accuracy data were available for the other two hs-cTn assays. The following subgroups were considered:

- age ≤ 70 years and age > 70 years
- patients with pre-existing CAD and patients without pre-existing CAD
- symptom onset at < 3 hours before presentation and symptom onset at ≥ 3 hours before presentation.

The subgroups with high pre-test probability and low-to-moderate pre-test probability were not considered, as the prevalence data for these subgroups were unknown.

Results of cost-effectiveness analyses

This section describes the results using probabilistic analyses for the base-case analysis and the secondary analysis. In addition, the sensitivity analyses (deterministic) and subgroup analyses are described (these deterministic analyses are also presented in tabulated form in *Appendices 5–9*.

Base-case analysis

The base-case analysis includes six test strategies. *Tables 17* and *18* show the probabilistic results of this analysis. Standard Tn testing was both most effective (15.101 LYs, 11.730 QALYs) and most expensive (£2697). The Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was least effective (15.076 LYs, 11.712 QALYs) and least expensive (£2253). Compared with standard Tn testing, hs-cTn testing resulted in ICERs ranging between £90,725 and £24,019 savings per QALY lost.

Comparisons based on the next best alternative showed that for willingness-to-pay values of < £6600 per QALY, the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, would be cost-effective. For thresholds between £6600 and £30,631 per QALY, the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective; above £30,631 per QALY the Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective. Standard Tn becomes cost-effective at a threshold of £90,725 or higher (see *Table 18*).

At willingness-to-pay thresholds of £20,000 and £30,000 per QALY, the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, had probabilities of being cost-effective of 47% and 35%, respectively. Although the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective at a willingness-to-pay threshold of £30,000 per QALY, the Abbott ARCHITECT hs-cTnI optimal strategy had the highest probability of being cost-effective (35%) at this threshold (*Figures 16* and *17*).

TABLE 17 Probabilistic results for base-case analysis: LYs

Strategy	LYs (95% CI)	Compared with standard Tn
Abbott ARCHITECT hs-cTnI (99th centile at presentation)	15.076 (14.321 to 15.764)	–0.024
Roche Elecsys hs-cTnT (99th centile at presentation)	15.085 (14.332 to 15.770)	–0.016
Beckman Coulter hs-cTnI (99th centile at presentation)	15.090 (14.338 to 15.774)	–0.010
Roche Elecsys hs-cTnT optimal strategy	15.091 (14.340 to 15.776)	–0.009
Abbott ARCHITECT hs-cTnI optimal strategy	15.098 (14.351 to 15.780)	–0.003
Standard Tn	15.101 (14.356 to 15.781)	

TABLE 18 Probabilistic results for base-case analysis: costs and QALYs

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs, £ (95% CI)	QALYs (95% CI)	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott ARCHITECT hs-cTnI (99th centile at presentation)	£2253 (£1702 to £2877)	11.712 (10.312 to 13.157)	–£444	–0.018	£24,019				
Roche Elecsys hs-cTnT (99th centile at presentation)	£2296 (£1731 to £2936)	11.718 (10.319 to 13.165)	–£401	–0.012	£33,247	Abbott ARCHITECT hs-cTnI (99th centile at presentation)	£42	0.006	Extendedly dominated
Beckman Coulter hs-cTnI (99th centile at presentation)	£2324 (£1755 to £2971)	11.723 (10.323 to 13.172)	–£373	–0.008	£48,337	Abbott ARCHITECT hs-cTnI (99th centile at presentation)	£71	0.011	£6600
Roche Elecsys hs-cTnT (optimal strategy)	£2422 (£1846 to £3077)	11.723 (10.326 to 13.171)	–£275	–0.007	£38,528	Beckman Coulter hs-cTnI (99th centile at presentation)	£98	0.001	Extendedly dominated
Abbott ARCHITECT hs-cTnI (optimal strategy)	£2491 (£1908 to £3148)	11.728 (10.328 to 13.177)	–£206	–0.002	£90,725	Beckman Coulter hs-cTnI (99th centile at presentation)	£167	0.005	£30,631
Standard Tn	£2697 (£2113 to £3359)	11.730 (10.334 to 13.179)				Abbott ARCHITECT hs-cTnI (optimal strategy)	£206	0.002	£90,725

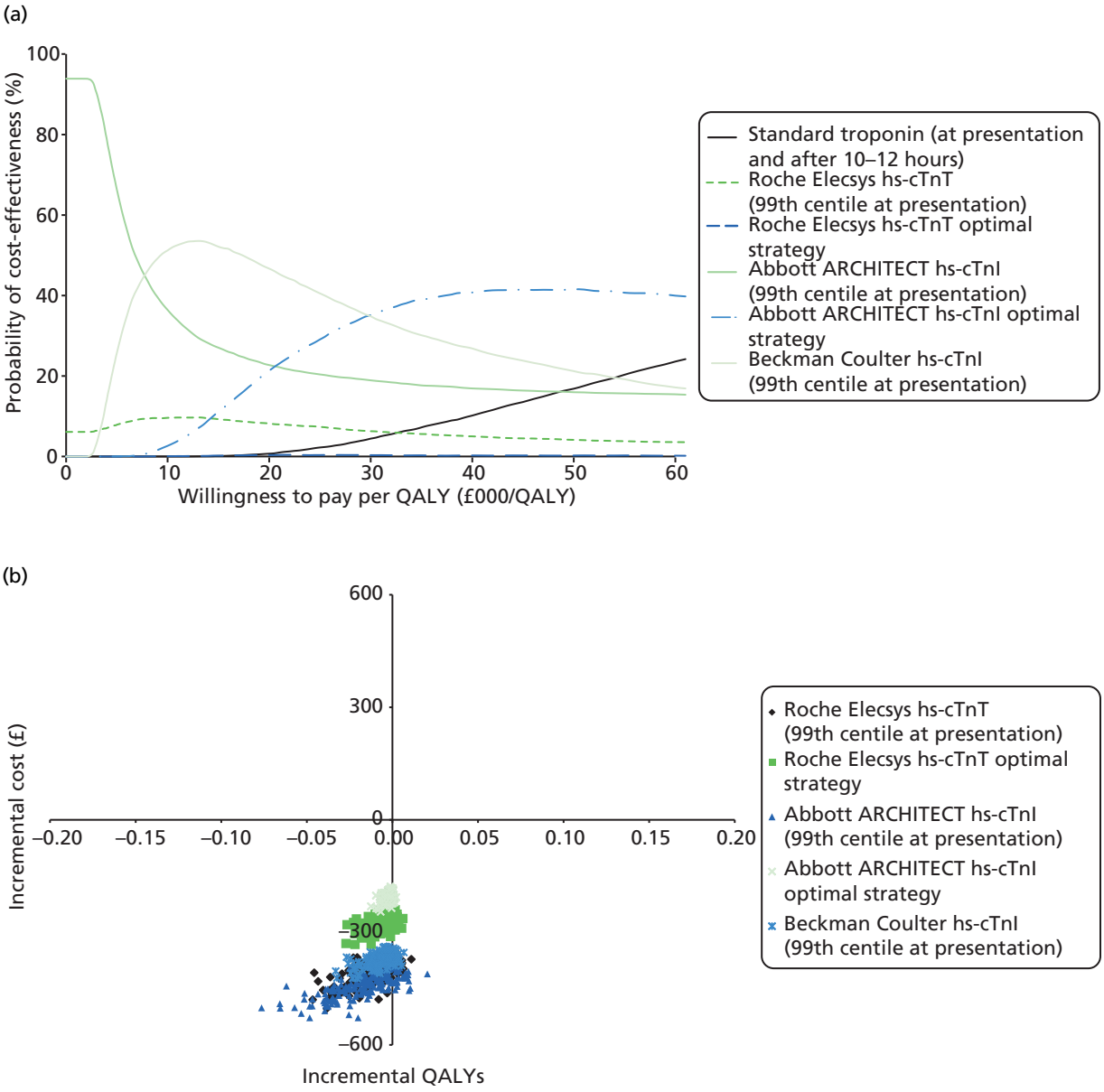

FIGURE 16 Cost-effectiveness acceptability curve and incremental cost-effectiveness plane (incremental costs and QALYs compared with standard Tn) for base-case analysis.

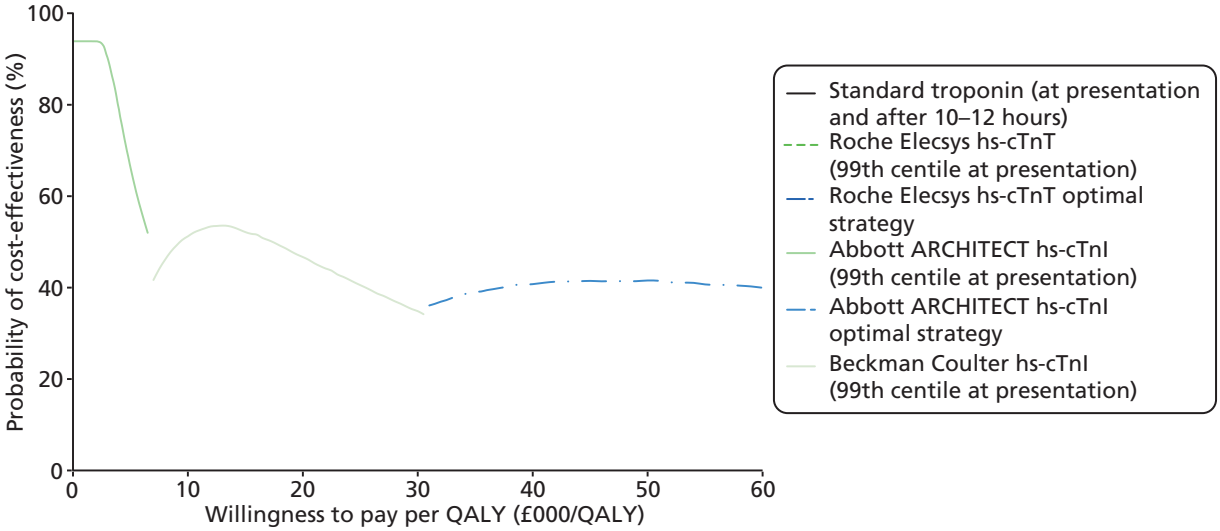

FIGURE 17 Cost-effectiveness acceptability frontier for base-case analysis.

Secondary analysis

The secondary analysis includes the same six test strategies. This analysis assumed that in a proportion of patients with a FP hs-cTn test (i.e. positive hs-cTn test and a negative standard Tn test), there is prognostic significance [i.e. it is associated with an increased risk of adverse events (mortality and re-infarction)].

Standard Tn testing was least effective (14.785 LYs, 11.464 QALYs) and most expensive (£3058). The Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was the least effective hs-cTn test strategy (14.833 LYs, 11.501 QALYs) and, overall, the least expensive strategy (£2781). The Abbott ARCHITECT hs-cTnI optimal strategy was most effective (14.855 LYs, 11.518 QALYs). Standard Tn testing was dominated by all hs-cTn testing strategies.

Comparisons based on the next best alternative showed that for willingness-to-pay values of < £13,623 per QALY, the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective. For thresholds between £13,623 and £14,562 per QALY, the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, was cost-effective; above £14,562 per QALY the Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective (*Tables 19* and *20*).

At willingness-to-pay thresholds of £20,000 and £30,000 per QALY, the Abbott ARCHITECT hs-cTnI optimal strategy had the highest probability of being cost-effective (53% and 67%, respectively; *Figures 18* and *19*).

TABLE 19 Probabilistic results for secondary analysis: LYs

Strategy	LYs (95% CI)	Compared with standard Tn
Abbott ARCHITECT hs-cTnI (99th centile at presentation)	14.833 (14.104 to 15.487)	0.048
Roche Elecsys hs-cTnI (99th centile at presentation)	14.837 (14.111 to 15.491)	0.052
Beckman Coulter hs-cTnI (99th centile at presentation)	14.839 (14.114 to 15.488)	0.054
Roche Elecsys hs-cTnT (optimal strategy)	14.843 (14.119 to 15.494)	0.058
Abbott ARCHITECT hs-cTnI (optimal strategy)	14.855 (14.129 to 15.502)	0.070
Standard Tn	14.785 (14.061 to 15.436)	

TABLE 20 Probabilistic results for secondary analysis: costs and QALYs

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs (95% CI)	QALYs (95% CI)	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott ARCHITECT hs-cTnI (99th centile at presentation)	£2781 (£2247 to £3388)	11.501 (10.087 to 12.918)	–£277	0.037	Dominant				
Roche Elecsys hs-cTnT (99th centile at presentation)	£2823 (£2271 to £3442)	11.504 (10.092 to 12.920)	–£235	0.040	Dominant	Abbott ARCHITECT hs-cTnI (99th centile at presentation)	£42	0.003	£13,623
Beckman Coulter hs-cTnI (99th centile at presentation)	£2851 (£2299 to £3477)	11.506 (10.093 to 12.923)	–£207	0.042	Dominant	Roche Elecsys hs-cTnT (99th centile at presentation)	£28	0.001	Extendedly dominated
Roche Elecsys hs-cTnT (optimal strategy)	£2949 (£2390 to £3579)	11.509 (10.095 to 12.926)	–£109	0.045	Dominant	Roche Elecsys hs-cTnT (99th centile at presentation)	£126	0.004	Extendedly dominated
Abbott ARCHITECT hs-cTnI (optimal strategy)	£3018 (£2446 to £3659)	11.518 (10.103 to 12.936)	–£39	0.054	Dominant	Roche Elecsys hs-cTnT (99th centile at presentation)	£196	0.013	£14,562
Standard Tn	£3058 (£2485 to £3708)	11.464 (10.053 to 12.869)				Abbott ARCHITECT hs-cTnI (optimal strategy)	£39	–0.054	Dominated

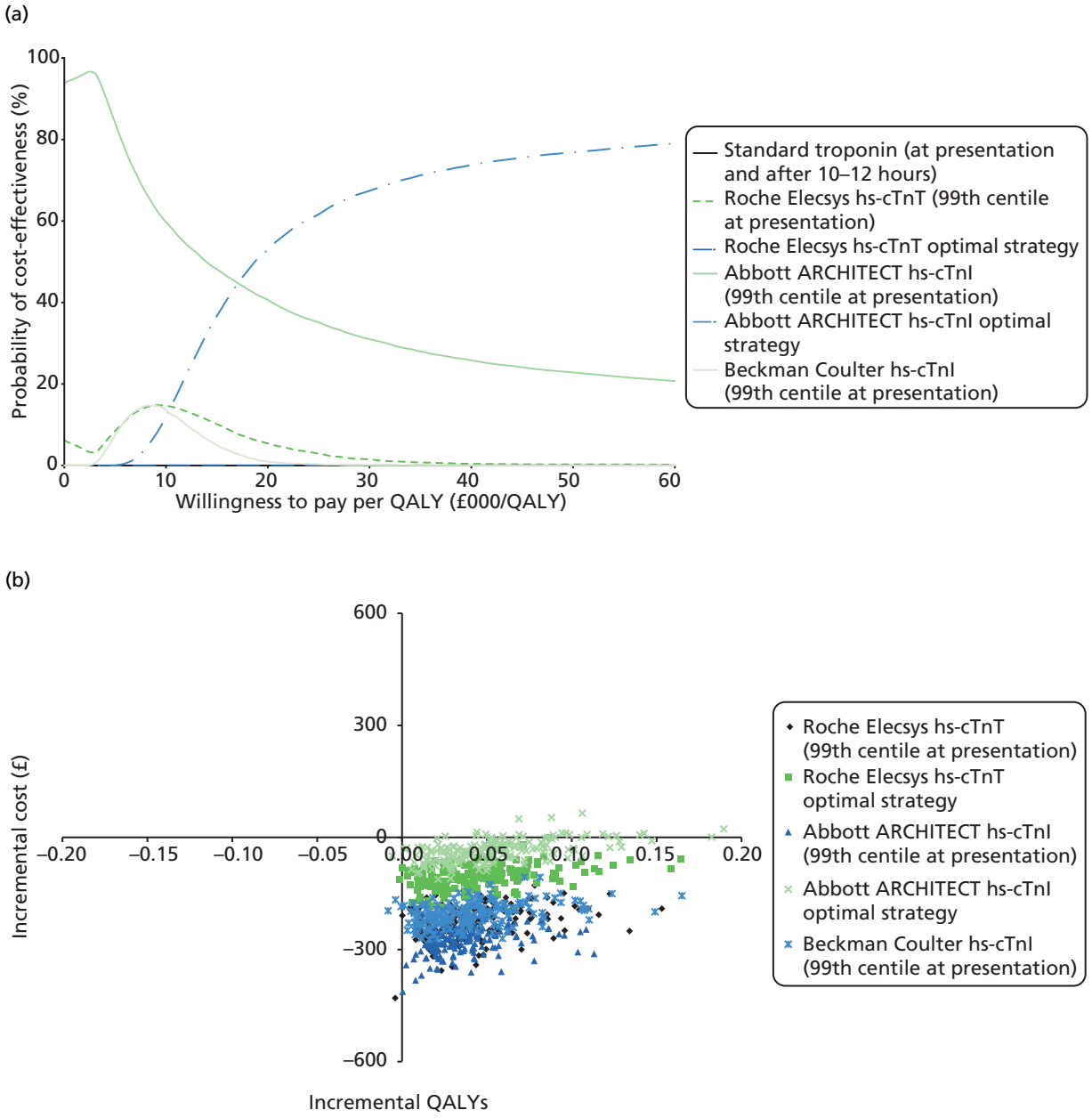

FIGURE 18 Cost-effectiveness acceptability curve and incremental cost-effectiveness plane (incremental costs and QALYs compared with standard Tn) for secondary analysis.

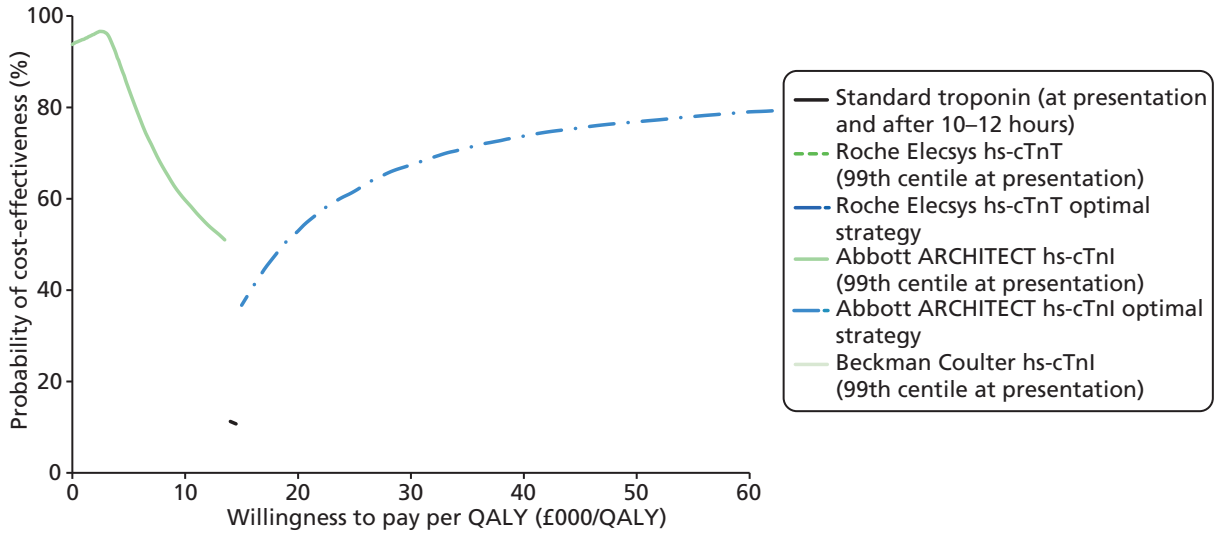

FIGURE 19 Cost-effectiveness acceptability frontier for secondary analysis.

Sensitivity analysis

The deterministic analysis for the base-case analysis is presented in *Appendix 5*. When it was assumed that the post-MI re-infarction and mortality probabilities would remain elevated for untreated AMI for a life-time period, the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds of < £1642 per QALY, at which point the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, became cost-effective up to a threshold of £7602 per QALY. The Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective for thresholds between £7602 and £26,532 per QALY. Standard Tn testing was cost-effective for thresholds of > £26,532 per QALY. Consistent with the base-case analysis, all 'no doctor on demand' sensitivity analyses (1, 2 or 3 hours) showed that the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds between approximately £8000 and £40,000 per QALY. Similarly, where the total delay decreased to 1.5 hours (and assuming availability of a doctor on demand), the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds between £7778 and £29,653 per QALY, at which point the ARCHITECT hs-cTnI optimal strategy became cost-effective. Adding AMI treatment costs for the patients with a FP test substantially impacted upon the results: standard Tn testing was cost-effective for all threshold values of > £16,050 per QALY. Adding AMI treatment costs to the UA health state for the first year had a negligible impact on the incremental outcomes.

The following input parameters had a noticeable impact on the estimated cost-effectiveness: 30-day mortality for treated and untreated AMI (decision tree) and the mortality RR for treated AMI compared with untreated AMI (Markov trace). Varying the remaining parameters did not have a substantial impact on the results (i.e. the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds between approximately £10,000 and £35,000 per QALY).

The deterministic analysis for the secondary analysis is presented in *Appendix 6*. When assuming that the post-AMI re-infarction and mortality probabilities would remain elevated for untreated AMI for a life-time period, the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds of < £1853 per QALY, at which point the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, became cost-effective up to a threshold of £2017 per QALY. The Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds between £2017 and £5889 per QALY. The Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective for thresholds of > £5889 per QALY. For all 'no doctor-on-demand' sensitivity analyses, the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds of < £18,000 per QALY for 1, 2 and 3 hours' delay. The Roche

Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds between £18,000 and £19,000, £20,000 and £22,000 per QALY in case of 1, 2 and 3 hours' delay, respectively. The Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective for higher thresholds. Similarly to the deterministic base case, for which the total delay decreased to 1.5 hours (assuming availability of a doctor on demand), the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds of below £14,956, at which point the ARCHITECT hs-cTnI optimal strategy became cost-effective. Adding AMI treatment costs for all patients with a FP test gave similar results to the deterministic analysis: the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for all threshold values of < £15,508 per QALY, at which point the Abbott hs-cTnI optimal strategy became the preferred option. Adding AMI treatment costs to the 'Unstable angina' health state for the first year had a negligible impact on the incremental outcomes.

The following input parameters had a noticeable impact on the estimated cost-effectiveness of the secondary analysis: increased test cost (of £40 per test), 30-day mortality for treated and untreated AMI (decision tree), and the re-infarction and mortality RR for treated AMI compared with untreated AMI (Markov trace). Varying the remaining parameters did not have a substantial impact on the results.

Subgroup analysis

Additional analyses were performed for subgroups based on age, sex, people with a history of previous NSTEMI, and AMI prevalence. These deterministic subgroup analyses (for the base case) analysis are presented in *Appendix 7*. Consistent with the base-case analyses, analyses based on age and sex subgroups indicated that, up to an age of 75 years, the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds between approximately £10,000 and £35,000 per QALY. The Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective for higher thresholds up to £115,000–170,000, at which point standard Tn testing became cost-effective. For females aged > 85 years, the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds between £15,793 and £74,597 per QALY; the Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective for thresholds between £74,597 and £259,592 per QALY, and standard Tn testing was cost-effective for thresholds of £259,592 per QALY and higher. For males aged > 85 years, the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds of < £28,711 per QALY; the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds between £28,711 and £143,225 per QALY and the Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective for thresholds between £143,225 and £503,476 per QALY, at which point standard Tn testing became cost-effective. The results for the subgroup with a history of previous NSTEMI were almost identical to the base-case analysis.

For subgroup analyses considering AMI prevalence, no testing was included as additional comparator. For an AMI prevalence of 1%, the no-testing strategy was cost-effective up to thresholds of £27,409 per QALY, at which point the Beckman Coulter hs-cTnI (99th centile) test became cost-effective up to a threshold of £447,934 per QALY. For an AMI prevalence of 5–20%, the no-testing strategy was cost-effective up to thresholds of £8759–11,703 per QALY, at which point the Beckman Coulter hs-cTnI (99th centile) test became cost-effective up to thresholds of £32,042–97,709 per QALY. For an AMI prevalence of 30%, the no-testing strategy was cost-effective up to a threshold of £8431 per QALY, at which point the Beckman Coulter hs-cTnI (99th centile) test became cost-effective up to a threshold of £24,745 per QALY. The Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective for thresholds between £24,745 and £70,942 per QALY.

In addition, cost-effectiveness estimates for the subgroups, described in *Chapter 3* (see *Presentation samples*), based on subgroup-specific accuracy and prevalence, are reported in *Appendix 9* (only comparing the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, and standard Tn testing). The results of these analyses indicated that differences in accuracy and AMI prevalence between subgroups had a substantial impact on the cost-effectiveness of the Roche Elecsys hs-cTnT assay

at presentation, using the 99th centile diagnostic threshold, compared with standard Tn testing (ICER range: £22,111–355,571; deterministic base case: £41,233).

The deterministic subgroup analyses for the secondary analysis are presented in *Appendix 8*. For females aged 45 years and males aged 45 or 55 years, the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds of < £16,023–17,836 per QALY. The Abbott ARCHITECT hs-cTnI optimal strategy became cost-effective for higher thresholds. For females aged 55 or 65 years and males aged 65 or 75 years, the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds of < £13,064–16,994 per QALY. From this threshold up to £18,999–25,149 per QALY, the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, was most cost-effective. The Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective for higher thresholds. For females aged 75 or 85 years, the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective up to thresholds of £12,392£21,140 per QALY, at which point the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, became cost-effective up to thresholds of £16,407–26,911 per QALY. The Abbott ARCHITECT hs-cTnI optimal strategy became cost-effective for thresholds of > £24,020–45,709 per QALY. For males aged 85 years, the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was cost-effective for thresholds of < £66,418 per QALY. The Abbott ARCHITECT hs-cTnI optimal strategy became cost-effective for higher thresholds.

For subgroup analyses considering AMI prevalence, no testing was included as additional comparator. For an AMI prevalence of 1%, the no-testing strategy was cost-effective up to a threshold of £4563 per QALY, at which point the Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, became cost-effective up to a threshold of £109,991 per QALY, where the Abbott ARCHITECT hs-cTnI optimal strategy became cost-effective. Similarly, for AMI prevalences of 5% and 10% the thresholds were £5209 and £35,574, and £5820 and £22,684, respectively. For a AMI prevalences of 20% and 30%, the Abbott ARCHITECT hs-cTnI optimal strategy was cost-effective for thresholds of > £16,319 and £15,410, respectively.

In contrast with the base-case analysis (described above), the subgroup-specific accuracy and prevalence (only comparing the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, and standard Tn testing) did not have an important impact on the cost-effectiveness (see *Appendix 9*). The Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, was dominant for all subgroups.

Chapter 5 Discussion

Statement of principal findings

Clinical effectiveness

All 18 studies[19,39,40,42,44,46,48,49,51,54,55,57,58,63,64,67,70,73] (37 publications[19,39,40–74]) included in the systematic review assessed the accuracy of one or more hs-cTn tests for the diagnosis of any AMI or for NSTEMI. There were no controlled trials comparing clinical outcomes in people assessed using hs-cTn tests to those assessed using conventional Tn assays. The majority (15/18) of the included studies reported data for the Roche Elecsys hs-cTnT assay; four studies[39,48,58,63] reported data for the Abbott ARCHITECT hs-cTnI assay and two studies[39,73] reported data for precommercial versions of the Beckman Coulter Access hs-cTnI assay. Not all of the included studies reported data on accuracy for the diagnosis of NSTEMI (i.e. for a population that excluded people with STEMI), which was the target population for this assessment. However, where data were available for both any AMI (population with symptoms suggestive of ACS) and NSTEMI (population which excluded people with STEMI), estimates of test performance were generally similar (see *Tables 4* and *6*).

When diagnosis was based on a single sample taken at presentation, using the 99th centile for the general population as the diagnostic threshold, positive LRs derived from summary estimates of sensitivity and specificity indicated that neither the Roche Elecsys hs-cTnT assay nor the Beckman Coulter Access hs-cTnI would be adequate to rule in a diagnosis of NSTEMI. The LR+ for the Roche Elecsys hs-cTnT assay was 5.41 (95% CI 3.40 to 8.63) and the LR+ for the Beckman Coulter Access hs-cTnI was 3.67 (95% CI 3.26 to 4.13). By contrast, the LR+ for the Abbott ARCHITECT hs-cTnI assay, in a population that did not exclude STEMI, was 11.47 (95% CI 9.04 to 16.19), indicating that a positive test using this assay may have some utility in confirming a diagnosis of AMI. The corresponding LR–s indicated that a negative test result on a single sample taken at presentation, using the 99th centile for the general population as the diagnostic threshold, would not be adequate to rule out NSTEMI using any of the three assays assessed. LR– was 0.15 (95% CI 0.08 to 0.26) for the Roche Elecsys hs-cTnT, 0.11 (95% CI 0.07 to 0.17) for the Beckman Coulter Access hs-cTnI, and 0.22 (95% CI 0.16 to 0.27) for the Abbott ARCHITECT hs-cTnI assay. Although these LRs are fairly low, the consequences of missing an AMI are so great that a test needs to be able to rule out an AMI with a very high degree of certainty. It should be noted that the Beckman Coulter hs-cTnI assay evaluated in the APACE study[39] was described as 'an investigational prototype'; the 99th centile (9 ng/l), described as 'according to the manufacturer', differs from the 99th centile given in the current product information leaflet (40 ng/l),[16] and from values reported in a conference abstract, (41 ng/l for the Access II analyser and 34 ng/l for the DxI analyser).[17] When a hypothetical cohort of 1000 people is considered, assuming a prevalence of NSTEMI of 17% [derived from studies included in our systematic review (see *Chapter 3*, *Presentation samples*)] the estimated number of people with AMI and a negative test result who would be erroneously discharged based on this testing protocol is 20 for the Roche Elecsys hs-cTnT assay, 14 for the Beckman Coulter Access hs-cTnI assay, and 34 for the Abbott ARCHITECT hs-cTnI assay.

Some limited data were available on the diagnostic performance of the Roche Elecsys hs-cTnT assay in clinical subgroups, using a single sample taken at presentation and the 99th centile diagnostic threshold. These data indicated a lower LR– when the test is used in certain population groups [e.g. people aged > 70 years LR– 0.05 (95% CI 0.02 to 0.18); people without pre-existing CAD LR– 0.07 (95% CI 0.04 to 0.16)] and with a high pre-test probability (determined by clinical judgement based on cardiovascular risk factors, type of chest pain, physical findings and ECG abnormalities; LR– 0.09, 95% CI 0.02 to 0.45). Using the hypothetical cohort of 1000 people described above, the estimated number of people with AMI and a negative test result who would be erroneously discharged if the test were used to rule out AMI in these selected populations is five for people aged > 70 years, 10 for people without pre-existing CAD, and 10 for people with a clinical assessment of high pre-test probability. When the performance of the Roche Elecsys

hs-cTnT assay was assessed in a population restricted to people who presented at > 3 hours after the onset of symptoms, a similar fall in the LR– was observed (LR– 0.08, 95% CI 0.05 to 0.11); the estimated number of people with AMI and a negative test result who would be erroneously discharged if the test were used to rule out AMI in this populations is 10.

We constructed optimal testing strategies for the Roche Elecsys hs-cTnT assay (see *Figure 9* and *Chapter 3*, *Diagnostic accuracy of the Roche Elecsys hs-cTnT assay*, *Multiple samples*) and for the Abbott ARCHITECT hs-cTnI assay (see *Figure 11* and *Chapter 3*, *Diagnostic accuracy of the Abbott ARCHITECT hs-cTnI assay*, *Multiple samples*). Both strategies use a two-step process, which provides two potential opportunities to rule out AMI and hence to discharge patients within the 4-hour window specified in the scope for this assessment. This potential is conditional upon the achievement of short (< 1 hour) turnaround times for hs-cTn testing, as recommended by the joint National Academy of Clinical Biochemistry and IFCC guidelines on Tn testing[101] and in line with clinical opinion; a study of 1355 ED physicians in the USA indicated that 75% believed that the results of Tn testing should be available to them within 45 minutes.[102] The initial step for both the Abbott ARCHITECT hs-cTnI optimal strategy and Roche Elecsys hs-cTnT optimal strategy was based on the use of an LoB (3 ng/l) diagnostic threshold in a sample taken at presentation and was selected for optimal rule-out potential (low LR–), regardless of poor rule-in performance. For the Roche Elecsys hs-cTnT optimal strategy, the second step involves an additional sample taken 2– 3 hours after admission and was selected to provide the best possible combination of rule-out and rule-in performance. Using the hypothetical cohort of 1000 people previously described, the initial step of the proposed Roche Elecsys hs-cTnT optimal strategy would result in discharge of 407 people, nine of whom would have been erroneously discharged with AMI. The second step of this strategy involves a combination of testing on admission and after 2 hours, where a negative result is defined as both no sample above the 99th centile AND a change of < 20% over 2 hours and provides the optimum rule-out performance (LR– 0.04, 95% CI 0.02 to 0.10); conversely, a positive result is defined as both a peak value above the 99th centile AND a change of > 20% over 2 hours and provides the optimum rule-in performance (LR+ 8.42, 95% CI 6.11 to 11.60). Application of the rule-out component of the second step would result in discharge of a further 286 people, five of whom would have been erroneously discharged. For the proposed Abbott ARCHITECT hs-cTnI optimal strategy, the initial rule-out step would result in discharge of 291 people, all of whom would have been appropriately discharged. The second step of this strategy involves repeat testing on a sample taken 3 hours after admission, using the 99th centile diagnostic threshold. Application of the rule-out component of the second step would result in discharge of a further 486 people, three of whom would have been erroneously discharged. Available data on the Beckman Coulter hs-TnI assay were insufficient to support construction of an optimal testing strategy.

Cost-effectiveness

The review of economic analyses of hs-cTn (i.e. either hs-cTnI or hs-cTnT) testing for the early rule-out of AMI in people with acute chest pain found four HTA reports, two full papers and one abstract. Based on all of these publications, it can be said that, in general, the question of whether hs-cTn testing is cost-effective cannot yet be answered unequivocally. The majority of papers reported substantial ICERs, with considerable uncertainty. In particular, the accuracy of high-sensitivity tests, as well as the efficiency of decision-making based on test results, were found to be important drivers of cost-effectiveness.

In our health-economic analysis, the cost-effectiveness of different testing strategies – involving hs-cTn for the early rule-out of AMI in people with acute chest pain presenting to the ED with suspected ACS and STEMI ruled out – was assessed. All analyses had the same comparator: standard Tn testing at 10–12 hours, which is considered the reference standard and therefore was assumed to have perfect sensitivity and specificity. In addition to the base-case analysis, given some evidence that FPs compared with this reference standard also have a poor prognosis, a secondary analysis was conducted, which assumed an increased adverse event risk for patients with FP hs-cTn tests. A number of subgroup and sensitivity analyses were also performed.

In the base-case analysis, standard Tn testing was both most effective and most costly. Strategies considered cost-effective depending upon ICER thresholds were Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold (thresholds of < £6597), Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold (thresholds between £6597 and £30,042), Abbott ARCHITECT hs-cTnI optimal strategy (LoD threshold at presentation, followed by 99th centile threshold at 3 hours) (thresholds between £30,042 and £103,194), and the standard Tn test (thresholds of > £103,194). The Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, and the Roche Elecsys hs-cTnT optimal strategy [LoB threshold at presentation followed by 99th centile threshold and/or Δ20% (compared with presentation test) at 1–3 hours] were extendedly dominated in this analysis (one of the more effective strategies was better value in that the ICER was lower).

In the secondary analysis, which assumed that a proportion of FPs in the hs-cTn testing strategies had an increased risk of adverse events, standard Tn was least effective and most costly and, therefore, a dominated strategy. The most effective strategy here was the Abbott ARCHITECT hs-cTnI optimal strategy. The Roche Elecsys hs-cTnT optimal strategy was extendedly dominated (one of the more effective strategies was better value in that the ICER was lower), as was the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, in this analysis. Strategies considered cost-effective were Abbott ARCHITECT hs-cTnI assay at presentation, using the 99th centile diagnostic threshold (thresholds of < £12,217), Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold (thresholds between £12,217 and £14,992), and Abbott ARCHITECT hs-cTnI optimal strategy (thresholds of > £14,992).

Sensitivity analyses showed that, in general, there were no major changes in the relative cost-effectiveness of strategies. That is, dominancy and order of relative cost-effectiveness were comparable, although the ICERs were different. Exceptions included assuming that the increased 30-day mortality for treated MI compared with untreated MI applied to a lifetime (instead of only during the first year after presentation at ED), which meant that standard Tn could be cost-effective from a threshold of ≥ £26,352. The same assumption applied to the secondary analysis meant that the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, was no longer extended dominated but was considered cost-effective at thresholds of between £2017 and £5889. Another sensitivity analysis that resulted in substantial changes was assigning AMI treatment costs to patients who tested FP. In the base case, under this assumption, standard Tn became cost-effective at an ICER threshold of £20,000 (ICER £16,050 compared with the Abbott ARCHITECT hs-cTnI optimal strategy). In the secondary analysis, however, assigning treatment costs to FP patients did not have an impact on the position of standard Tn; it was still dominated by another strategy (i.e. less effective and more costly).

Subgroup analyses (with non-subgroup specific accuracy data) for the base case showed that ICERs compared with the next best strategy were slightly higher for males at all ages. Also, for both females and males, ICERs increased with age. In addition, from ages ≥ 55 years (base case 53 years), the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, became extendedly dominated. In the subgroup with previous NSTEMI, again the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, was extendedly dominated, and ICERs are slightly higher than in the whole group. Subgroup analysis based on MI prevalence (including a no-testing strategy) indicated that only when MI prevalence is as low as 1% (base case 17%) was the no-testing strategy considered cost-effective up to an ICER threshold of £27,409, after which the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, strategy takes over. The higher the prevalence, the lower the point at which the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, strategy became cost-effective (i.e. £11,703 for prevalence 5%, £9740 for prevalence 10%, and £6597 for 17%).

For the secondary analysis, again, the ICERS for males were slightly higher than for females. For the various age categories, results were rather diffuse, but, as in the base case, ICERs appeared to increase with age. There did not appear to be a substantial difference between the MI prevalence subgroups [i.e. the no-testing strategy was cost-effective only up to rather modest ICER thresholds (£4563–7109) for all values of prevalence].

The subgroup analyses using subgroup-specific accuracy and prevalence could be performed for only the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, as there were no subgroup data on Beckman Coulter hs-cTnI and Abbott ARCHITECT hs-cTnI assays. The comparator was the standard Tn at 10–12 hours, which was assumed to have perfect sensitivity and specificity. For the base case, the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, was always less costly and less effective, but ICERs were more favourable for the following subgroups compared with their counterparts: age ≤ 70 years, with pre-existing CAD, and symptom onset at < 3 hours. For the secondary analysis, the standard Tn was dominated by the Roche Elecsys hs-cTnT assay at presentation, using the 99th centile diagnostic threshold, overall, as this test was both less costly and more effective. However, the subgroups that rendered the highest savings per QALY gained were consistent with the base-case analysis (i.e. age ≤ 70 years, with pre-existing CAD, and symptom onset at < 3 hours). Although data are lacking, it seems likely that these differences between subgroups can be extrapolated, at least partly, to the other tests considered in the base-case analysis.

Strengths and limitations of assessment

Clinical effectiveness

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,[103] search strategies were developed to maximise sensitivity at the expense of reduced specificity. Thus, large numbers of citations were identified and screened, relatively few of which met the inclusion criteria of the review.

The possibility of publication bias remains a potential problem for all systematic reviews. Considerations may differ for systematic reviews of test accuracy studies. It is relatively simple to define a positive result for studies of treatment, for example a significant difference between the treatment and control groups that favours treatment. This is not the case for test accuracy studies, which measure agreement between index test and reference standard. It would seem likely that studies finding greater agreement (high estimates of sensitivity and specificity) will be published more often. In addition, test accuracy data are often collected as part of routine clinical practice, or by retrospective review of records; test accuracy studies are not subject to the formal registration procedures applied to RCTs and are therefore more easily discarded when results appear unfavourable. The extent to which publication bias occurs in studies of test accuracy remains unclear; however, simulation studies have indicated that the effect of publication bias on meta-analytic estimates of test accuracy is minimal.[104] Formal assessment of publication bias in systematic reviews of test accuracy studies remains problematic and reliability is limited.[27] We did not undertake a statistical assessment of publication bias in this review. However, our search strategy included a variety of routes to identify unpublished studies and resulted in the inclusion of a number of conference abstracts.

Clear inclusion criteria were specified in the protocol for this review, a copy of which is available on the PROSPERO website (registration number CRD42013005939). The eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for exclusion for all of the studies which were considered potentially relevant at initial citation screening and were subsequently excluded on assessment of the full publication (see *Appendix 4*). The review process followed recommended methods to minimise the potential for error and/or bias;[25] studies were independently screened for inclusion by two reviewers, and data extraction and quality assessment were done by one reviewer and checked by a second (MW and PW). Any disagreements were resolved by consensus.

Studies included in this review were assessed for risk of bias and applicability using the QUADAS-2 tool developed by the authors[33] and recommended by the Cochrane Collaboration.[27] QUADAS-2 is structured into four key domains covering participant selection, index test, reference standard, and the flow of patients through the study (including timing of tests). Each domain is rated for risk of bias (low, high or unclear); the participant selection, index test and reference standard domain are, also, separately rated for concerns regarding the applicability of the study to the review question (low, high or unclear). The results of the QUADAS-2 assessment are reported, in full, for all included studies in *Appendix 3* and are summarised in *Chapter 3* (see *Study quality*). The main potential sources of bias in the studies included in this assessment were related to patient spectrum and patient flow (QUADAS domains 1 and 4). Reporting of the participant selection process was frequently unclear; a further study[55] was rated as unclear for this domain as a large number of patients were not enrolled as a result of 'technical reasons' that were not fully defined and so it was not possible to judge whether or not these comprised inappropriate exclusions. The most common feature of studies rated as 'high risk of bias' for patient selection was the inclusion of participants based on staffing or work flow considerations; for example, participants were excluded if they presented at night or during busy periods.[42,46,51] All ratings of 'high risk of bias' for patient flow were due to high proportions of withdrawals. There were also concerns regarding the applicability of the patient population and the reference standard in some of the included studies. The main area of concern, with respect to population, was for studies that enrolled mixed populations (i.e. when the target condition was any AMI); because the primary focus of this assessment was the diagnosis of NSTEMI in populations where patients with STEMI were excluded (i.e. target condition NSTEMI), the primary focus was the population of patients with STEMI excluded, mixed population studies that were not restricted to this specific patient group were considered to have high concerns regarding applicability. However, as noted above (see *Clinical effectiveness*), where data were available for both any AMI (mixed population) and NSTEMI (population which excluded people with STEMI), estimates of test performance were generally similar. In accordance with current NICE guidance,[11] our review question specified that an appropriate reference standard had to include a standard Tn measurement at baseline and at 10–12 hours after the onset of symptoms in 80% of the population. Although studies generally included a baseline and a second, later, standard Tn measurement, only five[19,39,42,51,63] met the specific timing criterion for the second standard Tn measurement; studies that did not meet this criterion were classified as having high concerns regarding applicability.

We identified one recently published systematic review which included an assessment of the accuracy of hs-cTn assays for the diagnosis of AMI and prediction of MACE.[7] This review, by Goodacre *et al.*,[7] also evaluated standard cTn assays (alone and in combination with other cardiac biomarkers) and the diagnostic accuracy of other cardiac biomarkers, as well as including prediction modelling studies, all of which were outside the scope of this assessment. Our systematic review represents an advance on Goodacre *et al.*,[7] as it provides a more up-to-date and comprehensive assessment of the performance of hs-cTn assays. Although the Goodacre review[7] was published in 2013, search dates were reported as 1995 to November 2010; hence it included only two studies,[57,72] which met the definition of a hs-cTn assay used in our assessment. Both of these studies[57,72] assessed the diagnostic performance of the Roche Elecsys hs-cTnT assay when applied to a single sample taken at presentation, using the 99th centile diagnostic threshold, and neither excluded participants with STEMI. Both studies[57,72] were also included in our systematic review and one study[57] contributed data to our summary estimates (based on a total of 15 studies) of the performance of the Roche Elecsys hs-cTnT assay for the diagnosis of any AMI at this threshold studies; the other[72] was an early publication of the APACE study, the most recent publication that contributed data to our main analysis (accuracy for the diagnosis of NSTEMI), which included a total of six studies.[39] The summary estimate of sensitivity derived from our systematic review was lower (88% for both any AMI or NSTEMI analyses) than that reported by the Goodacre review (96% for any AMI),[7] and our summary estimate of specificity was higher (82% for any AMI and 84% for NSTEMI) than that reported by the Goodacre review[7] (72% for any AMI). A more recent systematic review, published as a conference abstract, reported summary estimates of the sensitivity and specificity of hs-cTn on an admission sample of 88% and 82%, respectively, based on data from 17 studies.[105] This review pooled data from different hs-cTn assays in one analysis and also included data from some studies that assessed

assays that do not meet the definition of a hs-cTn assay used in our assessment. Despite these limitations, the summary estimates of sensitivity and specificity matched the summary estimates from our review for the performance of the Roche Elecsys hs-cTnT assay for the diagnosis of any AMI; this is unsurprising, as 13 of the 17 studies included in the analysis assed the Roche Elecsys hs-cTnT assay, using the 99th centile diagnostic threshold.[105] Our assessment represents an advance on both of these systematic reviews in that we provide up-to-date estimates of the diagnostic performance of assays meeting a strict definition for hs-cTn, which are stratified by hs-cTn assay type, diagnostic threshold and timing of the Tn test.

We believe that our assessment provides information of direct relevance to UK clinical practice as we focus on the performance of hs-cTn within the 4-hour time window corresponding to the target for NHS EDs, which specifies that 'no one should be waiting more than four hours in the ED from arrival to admission, transfer or discharge'.[89] Furthermore, we have used the data from our systematic review to propose strategies for how hs-cTn assays might be applied and interpreted in order to maximise diagnostic performance. These strategies were devised with consideration to test timing, diagnostic threshold and interpretation of combinations of multiple test results. One limitation of this approach is that our estimates of the effectiveness and cost-effectiveness of the proposed two-step strategies require the assumption that the diagnostic performance of the second step is the same when used in people in whom NSTEMI is not ruled out by the first step as it is when used in the whole population (see *Chapter 3*, *Diagnostic accuracy of the Roche Elecsys hs-cTnT assay*, *Multiple samples*, and *Diagnostic accuracy of the Abbott ARCHITECT hs-cTnI assay*, *Multiple samples*). This assumption was necessary because no combined test performance data were available for the proposed strategies. However, it can be argued that the assumption is reasonable as the first step in both strategies focuses on rule-out performance and thus has a low LR+. This means that there is a relatively small change in the prevalence of AMI between the first and second steps (17–27% for the Roche Elecsys hs-cTnT optimal strategy and 17–24% for the Abbott ARCHITECT hs-cTnI optimal strategy).

Our assessment was less comprehensive for the Abbott ARCHITECT hs-cTnI assay and the Beckman Coulter hs-cTnI assay than for the Roche Elecsys hs-cTnT, because available data were limited for these two assays.

Cost-effectiveness

Our cost-effectiveness analysis is the most comprehensive to date in terms of the number of relevant hs-cTn test strategies for the early rule-out of AMI in people presenting to the ED with acute chest pain and suspected ACS. Moreover, the de novo probabilistic model was based on one previously developed for a published and peer reviewed HTA.[80] This model was also used in a later assessments on the cost-effectiveness of biomarkers in patients with suspected ACS.[19] For the present analysis, a number of adjustments were made to the model, but most of the assumptions were maintained.

The model was also informed by a comprehensive, high-quality, systematic review of DTA. Additional parameters were either those from the original HTA model, or any of the further assessments, or, where necessary, were based on a pragmatic literature review. Such a review is standard practice in economic modelling given the large number of parameters required and we expect that the review has delivered the most relevant information given that it focused on identifying the most recent large UK-based studies.

As in any economic model, a number of major and minor assumptions had to be made. It is important to understand the impact of these assumptions in order to interpret correctly the results of the model. The impact of most assumptions has been explored in sensitivity and secondary analyses. However, one major assumption that was maintained throughout all analyses was the conservative assumption of no health benefit of early treatment in the hs-cTn strategies compared with 'late' treatment in the standard cTn strategy. Although many experts believe that there must be a benefit, at least to some extent, of treating patients early, there is no evidence to support or quantify a timing effect, as yet. In addition, there may well also be adverse effects associated with early treatment also (e.g. the risk of bleeding, unnecessary percutaneous coronary interventions, etc.). The Canadian HTA report[82] identified in the economic review

(see *Chapter 4*, *Canadian Agency for Drugs and Technologies in Health optimal use report*) did include an advantage for early treatment compared with late treatment, based on one study,[106] which investigated the effect of a 36-hour treatment delay. The RR found in this study[106] was then recalculated, assuming a constant effect of timing on treatment benefit, to a RR of 1.035 of mortality for a treatment delay of 6 hours compared with early treatment, was again adjusted to 1.01 based on expert opinion. Any possible adverse effect of early treatment was not considered in this analysis. A similar approach would have been possible in the present model, but, in our view, this would not be informative, given the level of uncertainty underlying this final estimate. Therefore, it was decided to leave out a possible effect of timing of treatment. This could be considered a conservative approach but even this is uncertain.

The assumption that standard Tn, as the reference standard, has perfect sensitivity and specificity was also maintained throughout all analyses. Although a simplification, given that the actual reference standard is standard Tn plus clinical information, this approach is consistent with previous modelling and incorporation of the effect of clinical information to the hs-cTn test would be very difficult, given the current lack of data. To some extent, clinical judgement might already be incorporated into the modelling because, for the effect of treatment (RR for re-infarction and mortality), the study performed by Mills *et al.*[83] was used. In this study,[83] not all patients with negative tests results were left untreated; we might therefore speculate that, where patients who tested negative were treated, this was because of clinical judgement. However, we cannot be certain that the observations from this trial reflect the true contribution of clinical judgement. On the other hand, there is recent evidence that the prognostic performance of standard Tn testing may be imperfect. For example, a negative Tn test might assess correctly that a patient is not experiencing a NSTEMI, but some patients with negative test results may still benefit from treatment. To take this possibility into account, a secondary analysis was performed, which resulted in the standard Tn strategy being dominated by the hs-cTn testing strategies. In other words, it seems reasonable to conclude that not only might hs-cTn be cost-effective, it might also be more effective than standard Tn.

Another assumption, which was varied in sensitivity analysis, with a rather substantial impact on results, was how to attribute costs of treatment to patients testing FP in the hs-cTn treatment strategies. In the base-case analysis, FP patients were assigned survival, quality of life, and costs of TN patients (i.e. they were basically assumed not to be treated). However, if hs-cTn assays were incorporated in clinical practice, patients with a positive result would be treated, at least up to the point where it is discovered they were FP. Therefore, in a sensitivity analysis, FP patients were assigned treatment costs as if they were TP, but mortality and quality of life as if they were TN. For the base case, this would change results quite dramatically, as the hs-cTn strategies would become more expensive but not more effective, whereas for the standard Tn nothing would change. For the secondary analysis (some hs-cTn FPs need and get treatment) things are different, as in this case treatment costs would be incurred for a proportion of patients (5%) but these patients would also receive the benefits of treatment. This approach had a very limited effect on results, in terms of strategies that were cost-effective. In our opinion, the secondary analysis, which assigns treatment costs to all FPs, but also assumes that some of these patients benefit treatment, is the most plausible scenario.

Uncertainties

Clinical effectiveness

The performance of any test that uses the 99th centile for the general population as the diagnostic threshold will be dependent upon the characteristics of the reference population from which this value was derived. Although the product information leaflet for the Abbott ARCHITECT hs-cTnI assay recommends that 'each laboratory should verify that the 99th centile is transferable to its population or establish its own 99th centile',[15] test accuracy data included in the assessment are predominantly based on the 99th centiles for the three assays (Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI, Beckman Coulter hs-cTnI) as reported by their respective manufacturers.[15,16,18] The 99th centile for the Roche Elecsys hs-cTnT was reported as being derived from a study population of 616 apparently healthy volunteers and blood

donors, with an age range of 20–71 years and equal proportions of males and females;[107] no further details were reported. The 99th centile for the Abbott ARCHITECT hs-cTnI assay was described as being derived from a study of '1,531 apparently healthy individuals in a US population with normal levels of BNP, HbA1c, and estimated GFR values'.[15] Although a 2012 'in press' reference for this study was given in the APACE study,[39] we were not able to identify any corresponding publication. It should also be noted that the Beckman Coulter hs-cTnI assay evaluated in the APACE study[39] was described as 'an investigational prototype'; the 99th centile (9 ng/l), described as 'according to the manufacturer', differs from the 99th centile given in the current product information leaflet (40 ng/l).[16] The product information leaflet describes this value as being derived from general practice samples obtained from London, UK, and the surrounding area; samples were from 1000 people aged > 40 years, with approximately equal numbers of males and females, and samples from people with abnormal urea and electrolytes, liver function tests, glucose or NT-proBNP (N-terminal pro-β-natiuretic peptide), were excluded.[16] Expected values, and hence diagnostic thresholds, derived from groups of healthy volunteers may have limited applicability to the population in whom hs-cTn testing would be applied in practice, for example with respect to age range. Data provided in the product information leaflets for the Roche Elecsys hs-cTnT assay and the Abbott ARCHITECT hs-cTnI assay both indicated that 99th centile values differed between males and females; the Abbott ARCHITECT hs-cTnI assay reported values of 15.6 ng/l and 34.2 ng/l for females and males, respectively,[15] and the Roche Elecsys hs-cTnT assay reported values of 10.0 ng/l and 14.2 ng/l for females and males, respectively.[18] Despite this, we were unable to identify any data on whether the diagnostic performance of tests varies according to sex, when a single common diagnostic threshold is used for both males and females; the effectiveness of using sex-specific diagnostic thresholds therefore remains uncertain. Similarly, we were unable to identify any data on the diagnostic performance of hs-cTn assays when used in people with impaired renal function.

Differences in the populations used to derive the 99th centile diagnostic threshold, and hence in the Tn level at which this threshold set, may also affect the ability of an assay to achieve the first point of the accepted definition of a hs-cTn assay (i.e. a CV of ≤ 10% at the 99th centile for the general population). A standardised definition of the required reference population would be useful in ensuring a 'level playing field' for classification of assays as 'high sensitive' and would aid comparisons between tests.

We identified some data on the diagnostic performance of hs-cTn testing in clinically important subgroups (older people,[39,53] and people with and without pre-existing CAD).[39,47] However, these data were very limited and were available only for the Roche Elecsys hs-cTnT assay. Therefore, there remains some uncertainty about how the diagnostic performance of individual hs-cTn assays may vary in clinically relevant subgroups, as well as what may constitute the optimal testing strategy in these groups.

A significant limitation of this assessment follows from the design of the primary studies included in the systematic review. The objective of these studies was to evaluate the diagnostic performance of hs-cTn assays when compared with a reference standard based on the universal definition of AMI endorsed by the ESC, the ACC, the AHA and the World Heart Federation (WHF).[8,21,22] The scope for this assessment did not include studies that evaluated the use of hs-cTn testing in combination with other tests, thus, studies that assessed the combined accuracy of a clinical risk score and a hs-cTn test used together would have been excluded; however, we did not identify any studies that were excluded on this basis. Studies assessing the diagnostic performance of a hs-cTn test alone, in which participants were subgrouped by clinical risk, met our inclusion criteria and were included in the systematic review. We identified only one study of this type,[49] which, as described above (see *Clinical effectiveness*), indicated that the rule-out performance of hs-cTnT testing may be improved if the test is used in a population with high clinically determined pre-test probability. There remains uncertainty around how hs-cTn testing would perform if used, as it would be in clinical practice, in combination with a clinical assessment of pre-test probability (with or without formal risk scoring). Full assessment of the independent predictive value of hs-cTn testing requires multivariable prediction modelling.

A final area of uncertainty exists with respect to the clinical significance of a 'FP' hs-cTn result [i.e. does a positive hs-cTn result imply a clinically important change in cardiac risk, when a diagnosis of AMI is not confirmed (based on standard Tns and the universal definition)]? Re-adjudication of the final diagnosis, using later hs-cTn measurements in place of the conventional Tn results, can provide some insight into this issue. The most recent publication from the APACE study[39] reported that when hs-cTnT results (including a 6-hour time point) were included in the reference standard diagnosis, this resulted in 131 participants being classified as having had a small AMI, which would have been classified as 'no AMI' where adjudication was based on standard Tn results.

Cost-effectiveness

The main uncertainties for the cost-effectiveness analysis lie in the model assumptions, particularly regarding the effect of actual clinical practice in terms of both other diagnostic information and treatment given this information. Although many of these assumptions have been varied in one-way sensitivity analysis, the precise implication of FN test results, where patients are discharged without essential treatment, or of FP test results, where patients stay in hospital and may receive unnecessary interventions, is unknown.

It should also be emphasised that the uncertainty resulting from the abovementioned assumptions was not parameterised in the model and is therefore not reflected in the PSAs or in the CEACs.

Chapter 6 Conclusions

Implications for service provision

We propose the use of two-step testing strategies to optimise the diagnostic performance of hs-cTn testing. There is evidence to suggest that undetectable levels of Tn (below the LoB/LoD of the assay) on presentation, measured using the Roche Elecsys hs-cTnT assay or the Abbott ARCHITECT hs-cTnI assay, may be sufficient to rule out NSTEMI in people presenting with symptoms that are suggestive of ACS. There is also evidence to suggest that a further rule-out step may be possible, within the 4-hour NHS ED target. For the Abbott ARCHITECT hs-cTnI assay, this second rule-out step would be based on a Tn level below the 99th centile in a sample taken 3 hours after presentation. For the Roche Elecsys hs-cTnT assay, the second rule-out step would be based on a Tn level below the 99th centile in all samples *and* a change in Tn level of < 20% between presentation and 2 hours. There is insufficient evidence to determine an optimal testing strategy for the Beckman Coulter hs-cTnI assay. There is some limited evidence to suggest that a Tn level below the 99th centile on presentation, measured using the Roche Elecsys hs-cTnT assay, may be sufficient to rule out NSTEMI in some groups (people aged > 70 years, people without pre-existing CAD and people with a clinically determined high pre-test probability).

When considering the base-case analysis it appears that the Beckman Coulter hs-cTnI assay at presentation, using the 99th centile diagnostic threshold, would be the cost-effective strategy, given an ICER threshold of £20,000–30,000. However, both cost and QALY differences between the strategies were small. This means that within the hs-cTn testing strategies, ICERs can change substantially especially with small changes in either costs or QALYs. Therefore, it is difficult to be confident that other hs-cTn strategies might not be cost-effective.

Overall, the model does not provide strong evidence to prefer one hs-cTn testing strategy over another. Results do, however, indicate that hs-cTn testing in general may be cost-effective compared with standard Tn testing. This becomes more likely if one assumes that hs-cTn testing detects some patients who require treatment despite their testing negative with standard Tn, as shown in the secondary analysis. In particular, the Abbott ARCHITECT hs-cTnI optimal strategy, which involves multiple testing and varying diagnostic thresholds, may be promising. The main issue, with regard to service provision, if implementation of a hs-cTn testing strategy is considered, is the balance between the likely reduction in cost and the risk of a reduction in effectiveness, albeit possibly small.

Suggested research priorities

Diagnostic cohort studies are needed to evaluate fully the performance of our proposed optimal testing strategies in a clinical setting.

If adoption of the Beckman Coulter hs-cTnI is to be considered, further studies are needed to evaluate fully the diagnostic accuracy of this test at the thresholds currently recommended by the manufacturer and to inform the development of an optimal testing strategy.

Further diagnostic cohort studies, or subgroup analyses of existing data sets, are needed to explore fully possible variation in the accuracy of hs-cTn assays and the optimal testing strategies for these assays in relevant demographic and clinical subgroups: sex; age; ethnicity; renal function; previous CAD; and previous AMI.

It is important to explore further the effects of clinical judgement (assessment of pre-test probability) on the diagnostic performance of hs-cTn testing. This could be achieved by assessing the combined diagnostic accuracy of risk scoring tools, such as TIMI or GRACE, and hs-cTn tests, or by assessing the accuracy of hs-cTn testing in subgroups stratified by pre-test probability.

Multivariable prediction modelling studies may be useful to assess the independent prognostic value of a positive hs-cTn test result, in the context of other clinical risk factors and tests.

As most of the uncertainties in the economic model were caused by assumptions relating to clinical effectiveness, this type of research would also facilitate economic analyses of hs-cTn testing.

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Contribution of authors

Marie Westwood and **Penny Whiting** planned and performed the systematic review and interpretation of evidence.

Thea van Asselt, **Bram Ramaekers**, **Praveen Thokala** and **Manuela Joore**, planned and performed the cost-effectiveness analyses and interpreted results.

Nigel Armstrong contributed to planning and interpretation of cost-effectiveness analyses, acquisition of input data and conducted model peer review.

Janine Ross devised and performed the literature searches and provided information support to the project.

Johan Severens and **Jos Kleijnen** provided senior advice and support to the systematic review and cost-effectiveness analyses, respectively.

All parties were involved in drafting and/or commenting on the report.

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Appendix 1 Literature search strategies

Clinical effectiveness search strategies

MEDLINE (OvidSP): 1946 to 2013/10/Week 1

Searched: 11 October 2013

1. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (229)
2. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni).ti,ab,ot. (99)
3. ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (563)
4. ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (349)
5. (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (769)
6. (troponin$ adj5 (architect or elecsys or accutni or accu-tni or access or unicel)).ti,ab,hw,ot. (66)
7. or/1-6 (1215)
8. troponin t/ or troponin I/ or (60304-72-5 or 77108-40-8).rn. (8642)
9. (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot. (4,878,300)
10. 8 and 9 (4209)
11. 7 or 10 (4559)
12. chest pain/ (9293)
13. ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (28,602)
14. exp myocardial ischemia/ (357,748)
15. (acute adj2 coronary adj2 syndrome$).ti,ab,ot. (16,495)
16. (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot. (285)
17. Unstable angina$.ti,ab,ot. (10,718)
18. ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest$ or occlusion$ or isch?emia$)).ti,ab,ot. (194,088)
19. (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI).ti,ab,ot. (53,168)
20. or/12-19 (444,673)
21. 11 and 20 (2503)
22. animals/ not (animals/ and humans/) (3,957,888)
23. 21 not 22 (2336)

MEDLINE In-Process & Other Non-Indexed Citations (OvidSP): up to 2013/10/01; MEDLINE Daily Update (OvidSP): up to 2013/10/01

Searched: 11 October 2013

1. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (32)
2. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni).ti,ab,ot. (9)
3. ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (62)
4. ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (29)
5. (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (99)

6. (troponin$ adj5 (architect or elecsys or accutni or accu-tni or access or unicel)).ti,ab,hw,ot. (3)
7. or/1-6 (125)
8. troponin t/ or troponin I/ or (60304-72-5 or 77108-40-8).rn. (5)
9. (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot. (388,942)
10. 8 and 9 (3)
11. 7 or 10 (127)
12. chest pain/ (13)
13. ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (1742)
14. exp myocardial ischemia/ (170)
15. (acute adj2 coronary adj2 syndrome$).ti,ab,ot. (1544)
16. (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot. (3)
17. Unstable angina$.ti,ab,ot. (378)
18. ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest$ or occlusion$ or isch?emia$)).ti,ab,ot. (8220)
19. (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI).ti,ab,ot. (4224)
20. or/12-19 (12,386)
21. 11 and 20 (76)
22. animals/ not (animals/ and humans/) (1462)
23. 21 not 22 (76)

EMBASE (OvidSP): 1974 to 2013/10/10

Searched: 11 October 2013

1. "high sensitivity cardiac troponin T"/ or high sensitivity troponin t assay/ (12)
2. "high sensitivity cardiac troponin I"/ or high sensitivity troponin i assay/ (3)
3. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (565)
4. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni).ti,ab,ot. (190)
5. ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (1052)
6. ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (598)
7. (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (1478)
8. (troponin$ adj5 (architect or elecsys or accutni or accu-tni or access or unicel)).ti,ab,hw,ot. (106)
9. or/1-8 (2142)
10. troponin t/ or troponin I/ or (60304-72-5 or 77108-40-8).rn. (18,661)
11. (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot,hw. (6,591,905)
12. 10 and 11 (9505)
13. 9 or 12 (10,097)
14. thorax pain/ (44,504)
15. ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (64,208)
16. acute coronary syndrome/ (24,295)
17. (acute adj2 coronary adj2 syndrome$).ti,ab,ot,hw. (34,428)
18. exp heart muscle ischemia/ (73,551)
19. exp heart infarction/ (266,027)
20. exp Unstable-Angina-Pectoris/ (16,552)
21. (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot,hw. (374)
22. Unstable angina$.ti,ab,ot. (14,593)

23. ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest$ or occlusion$ or isch?emia$)).ti,ab,ot,hw. (406,203)
24. (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI).ti,ab,ot,hw. (85,655)
25. or/14-24 (498,902)
26. 13 and 25 (6007)
27. animal/ (1,890,932)
28. animal experiment/ (1,720,343)
29. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5,825,865)
30. or/27-29 (5,825,865)
31. exp human/ (15,014,990)
32. human experiment/ (317,206)
33. or/31-32 (15,016,431)
34. 30 not (30 and 33) (4,642,837)
35. 26 not 34 (5642)
36. limit 35 to yr="2005 -Current" (4374)
37. remove duplicates from 36 (4282)

Cochrane Database of Systematic Reviews (CDSR) (Wiley), Issue 10/October, up to 2013/10/11; Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley), Issue 9/September, 2013; Database of Abstracts of Reviews of Effects (DARE) (Wiley), Issue 3/July, 2013; Health Technology Assessment Database (HTA) (Wiley), Issue 3/July:2013; NHS Economic Evaluation Database (NHS EED) (Wiley), Issue 3/July, 2013

Searched: 11 October 2013

1. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs):ti,ab,kw (5)
2. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni):ti,ab,kw (5)
3. ((troponin t or tnt or ctnt or tropt or trop t) near/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive)):ti,ab,kw (12)
4. ((troponin I or tni or ctni or tropI or trop I) near/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive)):ti,ab,kw (10)
5. (troponin* near/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive)):ti,ab,kw (27)
6. (troponin* near/5 (architect or elecsys or accutni or accu-tni or access or unicel)):ti,ab,kw (2)
7. #1 or #2 or #3 or #4 or #5 or #6 (42)
8. MeSH descriptor: [Troponin T] this term only (265)
9. MeSH descriptor: [Troponin I] this term only (309)
10. #8 or #9 (543)
11. (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive):ti,ab,kw (170,016)
12. #10 and #11 (236)
13. #7 or #12 (249)
14. MeSH descriptor: [Chest Pain] this term only (335)
15. ((chest or thorax or thoracic) near/2 (pain* or discomfort or tight* or pressure)):ti,ab,kw (1793)
16. (acute near/2 coronary near/2 syndrome*):ti,ab,kw (1678)
17. MeSH descriptor: [Myocardial Ischemia] explode all trees (20,427)
18. (preinfarc* Angina* or pre infarc* Angina*):ti,ab,kw (90)
19. (Unstable angina*):ti,ab,kw (1818)

20. ((heart* or myocardi* or cardiac or coronary) near/2 (preinfarc* or infarc* or attack* or arrest* or occlusion* or isch?emia*)):ti,ab,kw (16,156)
21. (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI):ti,ab, kw (4740)
22. #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 (28,923)
23. #13 and #22 from 2005 to 2013 (114)

CDSR search retrieved 0 references; CENTRAL search retrieved 108 references; DARE search retrieved 2 references; HTA search retrieved 1 references; NHS EED search retrieved 3 references.

Science Citation Index – Expanded (SCI) (Web of Science): 1970–2013/10/14; Conference Proceedings Citation Index (CPCI-S) (Web of Science): 1990–2013/10/14

Searched: 14 October 2013

Databases = SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan = 2005–13

1. 228 TS=(Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs)
2. 90 TS=(Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni)
3. 1438 TS=((troponin* or tnt or ctnt or tropt or tni or ctni or tropI or "trop t" or "trop I") NEAR/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or "high performance" or ultrasensitive))
4. 1470 #3 OR #2 OR #1
5. 13,963 TS=((chest or thorax or thoracic) NEAR (pain* or discomfort or tight* or pressure))
6. 19,298 TS=(acute NEAR/2 coronary NEAR/2 syndrome*)
7. 393 TS=(preinfarc* angina* or pre infarc* angina)
8. 5481 TS=unstable angina*
9. 115,395 TS=((heart* or myocard* or cardiac or coronary) NEAR/2 (preinfarc* or infarc* or attack* or arrest* or occlusion* or isch?emia*))
10. 40,133 TS=(MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI)
11. 155,342 #10 OR #9 OR #8 OR #7 OR #6 OR #5
12. 835 #11 AND #4

Latin American and Caribbean Health Sciences (LILACS): 1982–2013/09/24 (http://regional.bvsalud.org/php/index.php?lang=en)

Searched: 14 October 2013

Terms	Records
(Troponin$ or MH:D05.750.078.730.825.925 or MH:D12.776.210.500.910.925 or MH: D12.776.220.525.825.925 or MH:D05.750.078.730.825.962 or MH:D12.776.210.500.910.962 or MH: D12.776.220.525.825.962 or MH:D05.750.078.730.825 or MH:D12.776.210.500.910 or MH: D12.776.220.525.825 or Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs or Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni)	247
Total	**247**

Spanish and Portuguese translations of MeSH terms identified using the DECS (Health Sciences Descriptors) thesaurus: http://decs.bvs.br/I/homepagei.htm.

International Network of Agencies for Health Technology Assessment (INAHTA): up to 2013/10/15 (www.inahta.org/Search2/?pub=1)

Searched: 15 October 2013

Search term	Results
Troponin	9
Elecsys	2
Architect	0
Accutni	0/1
unicel	0
Total	**11**

BIOSIS Previews (Web of Knowledge): 1956–2013/10/11

Searched: 14 October 2013

1. Databases=BIOSIS Previews Timespan=2005-2013
2. 266 TS=(Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs)
3. 114 TS=(Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni)
4. 1055 TS=((troponin* or tnt or ctnt or tropt or tni or ctni or tropI or "trop t" or "trop I") NEAR/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or "high performance" or ultrasensitive))
5. 1095 #3 OR #2 OR #1
6. 7468 TS=((chest or thorax or thoracic) NEAR (pain* or discomfort or tight* or pressure))
7. 11,149 TS=(acute NEAR/2 coronary NEAR/2 syndrome*)
8. 196 TS=(preinfarc* angina* or pre infarc* angina)
9. 3025 TS=unstable angina*
10. 62,717 TS=((heart* or myocard* or cardiac or coronary) NEAR/2 (preinfarc* or infarc* or attack* or arrest* or occlusion* or isch?emia*))
11. 28,931 TS=(MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI)
12. 83,999 #10 OR #9 OR #8 OR #7 OR #6 OR #5
13. 628 #11 AND #4

National Institute for Health Research Health technology Assessment (Internet) (www.hta.ac.uk/) up to 2013/10/14

Searched: 14 October 2013

Browsed with Troponin terms – six results.

Aggressive Research Intelligence Facility (Internet): 1996–2013/10/16 (www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/databases/index.aspx)

Searched: 16 October 2013

Search terms	Quick search
Troponin*	21
Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs	0
Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni	0
Total	**21**

Medion database: up to 2013/10/16 (www.mediondatabase.nl/)

Searched: 16 October 2013

Searched: in 'Whole Database'

Search term in 'topics'	Results
Troponin	0
Troponins	0
Total	**0**

PROSPERO (International Prospective Register of Systematic Reviews) (Internet): up to 2013/10/10 (www.crd.york.ac.uk/prospero/)

Searched: 10 October 2013

Searched: in 'All fields'

Terms	Records
Troponin*	8
Total	**8**

Clinicaltrials.gov (Internet) (http://clinicaltrials.gov/ct2/search/advanced)

Searched: 14 October 2013

Advanced search option – search terms box.

Search terms	Condition	Intervention	Records
Troponin% AND (sensitiv% OR hs OR early OR initial OR rapid OR present% OR ultra OR high performance OR ultrasensitive OR elecsys OR architect OR accutni OR access OR unicel)			**186**
		Troponin%	**109**
(Hstnt OR hs-tnt OR hsctnt Or hs-ctnt OR tnt-hs OR tnths OR ctnths OR ctnt-hs OR Hstni OR hs-tni OR hsctni OR hs-ctni OR tni-hs OR tnihs OR ctnihs OR ctni-hs OR ctni-ultra OR accutni OR accu-tni)			**17**
Total			**312**

metaRegister of Controlled Trials (mRCT) (Internet) (www.controlled-trials.com/)

Searched: 10 October 2013

Search terms	Results
(troponin* AND (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive))	333
Total	**333**

WHO International Clinical Trials Registry Platform (ICTRP) (Internet) (www.who.int/ictrp/en/)

Searched: 10 October 2013

Advanced search option

Date of registration limited to 01/01/2005 to 10/10/2013

Title	Condition	Intervention	Records
Troponin OR Troponins			**67**
		Troponins	**2**
		Troponin	This search does not work – the results are irrelevant and do not contain the word troponin in the intervention field
Total			**69**

American Heart Association: Scientific Sessions (http://my.americanheart.org/professional/Sessions/ScientificSessions/Archive/Archive-Scientific-Sessions_UCM_316935_SubHomePage.jsp)

Searched: 29 October 2013

2013: Conference not yet taken place at time of searching

2012: http://circ.ahajournals.org/content/vol126/21_MeetingAbstracts

2011: http://circ.ahajournals.org/content/vol124/21_MeetingAbstracts

2010: http://circ.ahajournals.org/content/vol122/21_MeetingAbstracts

2009: http://circ.ahajournals.org/content/120/21/2152.full.pdf

Keyword	2013	2012	2011	2010	2009	Total
Troponin*	N/A	138	131	109	1	379

American Association for Clinical Chemistry (www.aacc.org/resourcecenters/meet_abstracts_archive/abstracts_archive/annual_meeting/Pages/default.aspx#)

Searched: 29 October 2013

2013 Abstracts from: Clinical Chemistry, 59(S10):A1–295
www.aacc.org/events/Annual_Meeting/abstracts/Documents/AACC_13_AbstractBook_Complete.pdf

2012 Abstracts from: Clinical Chemistry, 58(S10):a1–A264
www.aacc.org/events/annualmtgdirectory/Documents/AACC_12_AbstractBook-Final-Complete.pdf

2011 Abstracts from: Clinical Chemistry, 57 (S10): A1–A235
www.aacc.org/events/annualmtgdirectory/documents/AACC_11_FullAbstract.pdf

2010 Abstracts from: Clinical Chemistry, 57 (6 Suppl): A1–276
www.aacc.org/events/annualmtgdirectory/Pages/2010PosterAbstracts.aspx#

2009 19–23 July, Chicago, IL, www.abstractsonline.com/viewer/searchAdvanced.asp?MKey={CA6D749E-BE20-4F85-899B-8A84E2268F72}&AKey={B08F832C-9D23-4F0B-96C3-3FA22F3D94A1}

Keyword	2013	2012	2011	2010	2009	Totals
Troponin	48	21	32	40	29	170

European Society of Cardiology (http://spo.escardio.org/abstract-book/search.aspx)

Searched: 29 October 2013

Keyword	2013	2012	2011	2010	2009	Total
Troponin	52	51	61	51	25	240
Troponins	2	1	2	1	2	8

Additional searches

Results sorted by Link Ranking (www.ncbi.nlm.nih.gov/pubmed/)

Searched: 10 December 2013

Nine of the included publications were not indexed on PubMed. Indexed publications were checked for errata and comments. For each reference, the first 20 references were retrieved by carrying out a Related Citations search using PubMed's similarity matching algorithm. These records were downloaded for screening. All related citations were checked against the EndNote Library to remove duplicates, and only new unique references were imported and screened = 58 records.

Reference	PMID	Result retrieved
Santalo[40]	23764266	20/131
Aldous[41]	22109535	20/145
Sanchis[42]	22877804	20/203
Haaf[43]	22623715	20/203
Eggers[44]	22456003	20/145
Reiter[45]	22044927	20/280
Aldous[46]	22291171	20/277
Potocki[47]	22337952	20/304
Keller[48]	22203537	20/300
Meune[108]	22014790	20/252
Freund[49]	21663627	20/142
Aldous[50]	21784766	20/254
Melki[51]	21428843	20/210
Reichlin[52]	21709058	20/162
Reiter[53]	21362702	20/261
Aldous[54]	21441390	20/251
Kurz[55]	20852870	20/207
Hochholzer[56]	21138939	20/138
Christ[57]	20932502	20/201
Parsonage[58]	Not in PubMed	
Collinson[59]	Not in PubMed	
Body[60]	Not in PubMed	
Melki[61]	Not in PubMed	
Aldous[62]	Not in PubMed	
Cullen[63]	23583250	20/133
Sebbane[64]	23816196	20/131
Irfan[65]	23870791	20/134
Collinson[19]	23597479	20/275
Reiter[66]	23514979	20/155
Body[67]	21920261	20/192

Reference	PMID	Result retrieved
Aldous[68]	21441393	20/174
Keller[69]	Not in PubMed	
Collinson[58]	Not in PubMed	
Saenger[70]	Not in PubMed	
Lippi[73]	Not in PubMed	
Hoeller[39]	23604180	20/107
Total		**640**
Following duplicate removal, number of records screened		**58**

Cost-effectiveness searches

MEDLINE (OvidSP): 1946 to 2013/10/Week 1

Searched: 18 October 2013

1. economics/ (27,116)
2. exp "costs and cost analysis"/ (182,544)
3. economics, dental/ (1866)
4. exp "economics, hospital"/ (19,403)
5. economics, medical/ (8578)
6. economics, nursing/ (3879)
7. economics, pharmaceutical/ (2605)
8. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (427,344)
9. (expenditure$ not energy).ti,ab. (17,552)
10. (value adj1 money).ti,ab. (22)
11. budget$.ti,ab. (17,208)
12. or/1-11 (551,693)
13. ((energy or oxygen) adj cost).ti,ab. (2752)
14. (metabolic adj cost).ti,ab. (798)
15. ((energy or oxygen) adj expenditure).ti,ab. (16,662)
16. or/13-15 (19,503)
17. 12 not 16 (547,348)
18. letter.pt. (803,396)
19. editorial.pt. (334,975)
20. historical article.pt. (299,710)
21. or/18-20 (1,423,597)
22. 17 not 21 (519,320)
23. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (229)
24. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni).ti,ab,ot. (99)
25. ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (563)
26. ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (349)
27. (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (769)
28. (troponin$ adj5 (architect or elecsys or accutni or accu-tni or access or unicel)).ti,ab,hw,ot. (66)

29. or/23-28 (1215)
30. troponin t/ or troponin I/ or (60304-72-5 or 77108-40-8).rn. (8642)
31. (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot. (4,878,300)
32. 30 and 31 (4209)
33. 29 or 32 (4559)
34. chest pain/ (9293)
35. ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (28,602)
36. exp myocardial ischemia/ (357,748)
37. (acute adj2 coronary adj2 syndrome$).ti,ab,ot. (16,495)
38. (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot. (285)
39. Unstable angina$.ti,ab,ot. (10,718)
40. ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest$ or occlusion$ or isch?emia$)).ti,ab,ot. (194,088)
41. (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI).ti,ab,ot. (53,168)
42. or/34-41 (444,673)
43. 33 and 42 (2503)
44. animals/ not (animals/ and humans/) (3,957,888)
45. 43 not 44 (2336)
46. limit 45 to yr="2005 -Current" (1457)
47. 22 and 46 (43)

Costs filter: Centre for Reviews and Dissemination. NHS EED Economics Filter: MEDLINE (Ovid) monthly search York: Centre for Reviews and Dissemination; 2010.

MEDLINE In-Process & Other Non-Indexed Citations (OvidSP): up to 2013/10/01, MEDLINE daily update: up to 2013/10/01

Searched: 18 October 2013

1. economics/ (2)
2. exp "costs and cost analysis"/ (87)
3. economics, dental/ (0)
4. exp "economics, hospital"/ (8)
5. economics, medical/ (0)
6. economics, nursing/ (0)
7. economics, pharmaceutical/ (1)
8. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (39,821)
9. (expenditure$ not energy).ti,ab. (1172)
10. (value adj1 money).ti,ab. (4)
11. budget$.ti,ab. (1822)
12. or/1-11 (41,689)
13. ((energy or oxygen) adj cost).ti,ab. (218)
14. (metabolic adj cost).ti,ab. (67)
15. ((energy or oxygen) adj expenditure).ti,ab. (911)
16. or/13-15 (1160)
17. 12 not 16 (41,354)
18. letter.pt. (24,293)
19. editorial.pt. (14,525)
20. historical article.pt. (68)
21. or/18-20 (38,878)

22. 17 not 21 (40,906)
23. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (32)
24. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni).ti,ab,ot. (9)
25. ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (62)
26. ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (29)
27. (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (99)
28. (troponin$ adj5 (architect or elecsys or accutni or accu-tni or access or unicel)).ti,ab,hw,ot. (3)
29. or/23-28 (125)
30. troponin t/ or troponin I/ or (60304-72-5 or 77108-40-8).rn. (5)
31. (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot. (388,942)
32. 30 and 31 (3)
33. 29 or 32 (127)
34. chest pain/ (13)
35. ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (1742)
36. exp myocardial ischemia/ (170)
37. (acute adj2 coronary adj2 syndrome$).ti,ab,ot. (1544)
38. (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot. (3)
39. Unstable angina$.ti,ab,ot. (378)
40. ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest$ or occlusion$ or isch?emia$)).ti,ab,ot. (8220)
41. (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI).ti,ab,ot. (4224)
42. or/34-41 (12,386)
43. 33 and 42 (76)
44. animals/ not (animals/ and humans/) (1462)
45. 43 not 44 (76)
46. limit 45 to yr="2005 -Current" (75)
47. 22 and 46 (4)

Costs filter: Centre for Reviews and Dissemination. NHS EED Economics Filter: MEDLINE (Ovid) monthly search. York: Centre for Reviews and Dissemination; 2010.

EMBASE (OvidSP): 1974 to 2013/10/17

Searched: 18 October 2013

1. health-economics/ (33,273)
2. exp economic-evaluation/ (205,882)
3. exp health-care-cost/ (197,503)
4. exp pharmacoeconomics/ (169,588)
5. or/1-4 (471,813)
6. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (590,127)
7. (expenditure$ not energy).ti,ab. (23,360)
8. (value adj2 money).ti,ab. (1320)
9. budget$.ti,ab. (23,595)
10. or/6-9 (613,918)
11. 5 or 10 (885,833)
12. letter.pt. (844,056)
13. editorial.pt. (449,323)
14. note.pt. (587,506)
15. or/12-14 (1,880,885)
16. 11 not 15 (799,169)
17. (metabolic adj cost).ti,ab. (876)
18. ((energy or oxygen) adj cost).ti,ab. (3163)
19. ((energy or oxygen) adj expenditure).ti,ab. (19,981)
20. or/17-19 (23,208)
21. 16 not 20 (794,101)
22. "high sensitivity cardiac troponin T"/ or high sensitivity troponin t assay/ (12)
23. "high sensitivity cardiac troponin I"/ or high sensitivity troponin i assay/ (3)
24. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (571)
25. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni).ti,ab,ot. (193)
26. ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (1059)
27. ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (602)
28. (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (1489)
29. (troponin$ adj5 (architect or elecsys or accutni or accu-tni or access or unicel)).ti,ab,hw,ot. (106)
30. or/22-29 (2155)
31. troponin t/ or troponin I/ or (60304-72-5 or 77108-40-8).rn. (18,726)
32. (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot,hw. (6,601,404)
33. 31 and 32 (9548)
34. 30 or 33 (10,144)
35. thorax pain/ (44,662)
36. ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (64,388)
37. acute coronary syndrome/ (24,412)
38. (acute adj2 coronary adj2 syndrome$).ti,ab,ot,hw. (34,558)
39. exp heart muscle ischemia/ (73,666)
40. exp heart infarction/ (266,475)
41. exp Unstable-Angina-Pectoris/ (16,570)
42. (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot,hw. (374)
43. Unstable angina$.ti,ab,ot. (14,604)

44. ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest$ or occlusion$ or isch?emia$)).ti,ab,ot,hw. (406,847)
45. (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI). ti,ab,ot,hw. (85,913)
46. or/35-45 (499,787)
47. 34 and 46 (6035)
48. animal/ (1,890,937)
49. animal experiment/ (1,721,607)
50. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5,828,979)
51. or/48-50 (5,828,979)
52. exp human/ (15,032,575)
53. human experiment/ (317,393)
54. or/52-53 (15,034,016)
55. 51 not (51 and 54) (4,644,866)
56. 47 not 55 (5669)
57. limit 56 to yr="2005 -Current" (4401)
58. remove duplicates from 57 (4309)
59. 21 and 58 (129)

Costs filter: Centre for Reviews and Dissemination. NHS EED Economics Filter: EMBASE (Ovid) weekly search. York: Centre for Reviews and Dissemination; 2010.

NHS Economic Evaluation Database (NHS EED) (Wiley) Issue 3/July:2013

Searched: 11 October 2013

1. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs):ti,ab,kw (5)
2. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or) accutni or accu-tni):ti,ab,kw (5)
3. ((troponin t or tnt or ctnt or tropt or trop t) near/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive)):ti,ab,kw (12)
4. ((troponin I or tni or ctni or tropI or trop I) near/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive)):ti,ab,kw (10)
5. (troponin* near/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive)):ti,ab,kw (27)
6. (troponin* near/5 (architect or elecsys or accutni or accu-tni or access or unicel)):ti,ab,kw (2)
7. #1 or #2 or #3 or #4 or #5 or #6 (42)
8. MeSH descriptor: [Troponin T] this term only (265)
9. MeSH descriptor: [Troponin I] this term only (309)
10. #8 or #9 (543)
11. (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive): ti,ab,kw (170,016)
12. #10 and #11 (236)
13. #7 or #12 (249)
14. MeSH descriptor: [Chest Pain] this term only (335)
15. ((chest or thorax or thoracic) near/2 (pain* or discomfort or tight* or pressure)):ti,ab,kw (1793)
16. (acute near/2 coronary near/2 syndrome*):ti,ab,kw (1678)
17. MeSH descriptor: [Myocardial Ischemia] explode all trees (20,427)
18. (preinfarc* Angina* or pre infarc* Angina*):ti,ab,kw (90
19. (Unstable angina*):ti,ab,kw (1818)
20. ((heart* or myocardi* or cardiac or coronary) near/2 (preinfarc* or infarc* or attack* or arrest* or occlusion* or isch?emia*)):ti,ab,kw (16,156)

21. (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI):ti,ab, kw (4740)
22. #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 (28,923)
23. #13 and #22 from 2005 to 2013 (114)

NHS EED search retrieved three references.

Health Economic Evaluation Database (HEED) (Internet): up to 2013/10/18 (http://onlinelibrary.wiley.com/book/10.1002/9780470510933)

Searched: 18 October 2013

Compound search, (all data), unable to limit by date

Troponin*

AND

sensitiv* OR hs OR early OR initial OR rapid OR present OR ultra OR high performance OR ultrasensitive OR elecsys OR architect OR accutni OR access OR unicel

N=20

Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs or Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra

N=0

Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni

N=0

EconLit (EBSCO) 1990–2013/09/01

Searched: 18 October 2013

Search modes – Boolean/Phrase

S1 TX Troponin* (0)

S2 TX Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs (0)

S3 TX Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni (0)

Science Citation Index Expanded (SCI) (Web of Science): 1970–2013/10/21, Conference Proceedings Citation Index (CPCI-S) (Web of Science): 1990–2013/10/21

Searched: 21 October 2013

1. 622,444 TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or budget*)
2. 10,144 TS=(expenditure* not energy)
3. 952 TS=(value NEAR money)
4. 626,873 #3 OR #2 OR #1
5. 22,383 TS=((energy or oxygen) NEAR cost)
6. 1804 TS=(metabolic NEAR cost)
7. 12,974 TS=((energy or oxygen) NEAR expenditure)
8. 35,684 #7 OR #6 OR #5
9. 602,398 #4 NOT #8
10. 230 TS=(Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs)
11. 91 TS=(Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni)
12. 1442 TS=((troponin* or tnt or ctnt or tropt or tni or ctni or tropI or "trop t" or "trop I") NEAR/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or "high performance" or ultrasensitive))
13. 1474 #12 OR #11 OR #10
14. 14,001 TS=((chest or thorax or thoracic) NEAR (pain* or discomfort or tight* or pressure))
15. 19,324 TS=(acute NEAR/2 coronary NEAR/2 syndrome*)
16. 393 TS=(preinfarc* angina* or pre infarc* angina)
17. 5486 TS=unstable angina*
18. 115,562 TS=((heart* or myocard* or cardiac or coronary) NEAR/2 (preinfarc* or infarc* or attack* or arrest* or occlusion* or isch?emia*))
19. 40,195 TS=(MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI)
20. 155,582 #19 OR #18 OR #17 OR #16 OR #15 OR #14
21. 839 #20 AND #13
22. 32 #21 AND #9

Databases = SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan = 2005–2013.

Research Papers in Economics (REPEC) up to 2013/10/21 (http://econpapers.repec.org/scripts/search/search.asp?pg=-1)

Searched: 21 October 2013

Advanced search

Free text search	Results	Total
Troponin	0/2	0
Troponins	0/1	0

Appendix 2 Data extraction tables

Baseline study details

Study details	Selection criteria	Participant details	Test manufacturer
Aldous (2012)[41,46,50] **Country:** New Zealand **Funding:** Funded by the National Heart Foundation of New Zealand and assay reagents were provided by the manufacturer (Roche). One author declared personal funding from Abbott **Recruitment:** November 2007 to December 2010 **Number of participants:** 939,[46] 385[41]	**Inclusion criteria:** Adults (≥ 18 years) with symptoms suggestive of cardiac ischaemia (acute chest, epigastric, neck, jaw or arm pain or discomfort or pressure without an apparent non-cardiac source) **Exclusion criteria:** ST segment elevation on ECG;[46] unable to provide informed consent; would not be available to follow-up **Patient category:** NSTEMI[46] Mixed[41]	**Median age (IQR), years:** 65 (56–76) **Male (%):** 60 **White (%):** 89 **Previous CAD (%):** 52 **Previous family history (%):** 60 **Previous revascularisation (%):** 30 **Diabetes (%):** 17 **Smoking (%):** 61 **Hypertension (%):** 61 **Dyslipidaemia (%):** 58 **Median BMI (IQR), kg/m²:** 28 (25–31) **Median (IQR) time to presentation (hours):** 6.3 (3.3–13.3)	Roche
Aldous (2011)[54,62,68] **Country:** New Zealand **Funding:** Manufacturers (Roche and Abbott) supplied assays. The study was funded by a New Zealand National Heart Foundation grant **Recruitment:** November 2006 to April 2007 **Number of participants:** 332	**Inclusion criteria:** Consecutive patients presenting to the ED with chest pain; participants were eligible for inclusion if the attending clinician had sufficient suspicion of ACS that serial Tns and ECGs were considered necessary **Exclusion criteria:** < 18 years; samples not stored for both time points (on admission and at 6–24 hours) **Patient category:** Mixed	**Median age (IQR), years:** 64 (53–74) **Male (%):** 60 **White (%):** 85 **Previous CAD (%):** 54 **Previous family history (%):** 40 **Diabetes (%):** 16 **Smoking (%):** 45 **Hypertension (%):** 46 **Dyslipidaemia (%):** 38 **Median (IQR) time to presentation (hours):** 4.0 (2.0 to 8.6)	Roche

Study details	Selection criteria	Participant details	Test manufacturer
Body (2011)[60,67,74] **Country:** UK **Funding:** Central Manchester NHS Trust **Recruitment:** January 2006 to February 2007 **Number of participants eligible (enrolled):** 1004 (703)	**Inclusion criteria:** Presenting to ED with chest pain; age > 25 years and chest pain within previous 24 hours that initial treating physician suspected may be cardiac in nature **Exclusion criteria:** Renal failure requiring dialysis, trauma with suspected myocardial contusion, or another medical condition mandating hospital admission or if they did not consent to and provide a blood sample for use by the research team **Patient category:** Mixed	**Mean age (SD), years:** 59 (14) **Male (%):** 61 **Kidney disease (%):** 1 **Previous AMI (%):** 24 **Previous family history (%):** 48 **Previous revascularisation (%):** 20 **Diabetes (%):** 18 **Smoking (%):** 31 **Dyslipidaemia (%):** 48 **Median time to presentation (hours):** 3.5	Roche
Christ (2010)[57] **Country:** Germany **Funding:** hs-cTnT test kits were provided by Roche **Recruitment:** 7 September 2009 to 21 September 2009 **Number of participants:** 137	**Inclusion criteria:** Consecutive patients with acute chest pain of possible coronary origin presenting to the emergency department **Exclusion criteria:** NR **Patient category:** Mixed	**Mean age (SD), years:** 66 (16) **Male (%):** 64 **Previous AMI (%):** 32 **Previous CAD (%):** 34 **Previous family history (%):** 12 **Previous revascularisation (%):** 24 **Diabetes (%):** 22 **Smoking (%):** 22 **Hypertension (%):** 66 **Dyslipidaemia (%):** 35 **Mean BMI (SD), kg/m^2:** 28 (5) **Time to presentation (hours):** 0–2, 36%; 2–6, 22%; 6–24, 33%; > 24, 20%	Roche

Study details	Selection criteria	Participant details	Test manufacturer
Collinson (2013)[19,58,59] **Country:** UK **Funding:** UK Health Technology Assessment programme **Study name:** Point-of-care arm of the RATPAC study **Recruitment:** February 2007 to June 2008 **Number of participants:** 850	**Inclusion criteria:** Patients presenting to the ED with chest pain attributable to suspected, but not proven, AMI **Exclusion criteria:** ECG changes diagnostic for AMI or high-risk ACS (> 1 mm ST deviation, or > 3 mm inverted T waves); known CAD with prolonged (> 1 hour) or recurrent typical cardiac-type pain; proven or suspected serious non-cardiac pathology (e.g. pulmonary embolism); comorbidity or social problems requiring hospital admission even if AMI ruled out; obvious non-cardiac cause of chest pain (e.g. pneumothorax or muscular pain); presentation > 12 hours after most significant episode of pain **Patient category:** NSTEMI	**Median age (IQR), years:** 54 (44 to 64) **Male (%):** 60 **Previous AMI (%):** 40 **Previous family history (%):** **Previous revascularisation (%):** 1 **Diabetes (%):** 8 **Smoking (%):** 28 **Hypertension (%):** 35 **Dyslipidaemia (%):** 24 **Median (IQR) time to presentation (hours):** 8.25 (5.17 to 12.30)	Roche
Cullen (2013)[63] **Countries:** New Zealand and Australia **Funding:** The manufacturers (Abbott, Roche and Siemens) provided partial funding **Study name:** ADAPT study (ACTRN12611001069943) **Recruitment:** November 2007 to February 2011 **Number of participants:** 1635	**Inclusion criteria:** Prospectively recruited adults with at least 5 minutes of possible cardiac symptoms in accordance with the AHA case definitions (acute chest, epigastric, neck, jaw or arm pain; or discomfort or pressure without a clear non-cardiac source) **Exclusion criteria:** Pregnancy; unable or unwilling to consent; recruitment inappropriate (e.g. terminal illness); transfer from another hospital; follow-up considered impossible (e.g. homeless patients) **Patient category:** Mixed	**Mean age (SD), years:** 59 (13) **Male (%):** 60 **Previous AMI (%):** 24 **Previous family history (%):** 57 **Previous revascularisation (%):** 8 **Diabetes (%):** 15 **Smoking (%):** 18 **Hypertension (%):** 52 **Dyslipidaemia (%):** 57 **Mean (SD) time to presentation (hours):** 22.3 (60.5)	Abbott

Study details	Selection criteria	Participant details	Test manufacturer
Eggers (2012)[44] **Country:** Sweden **Funding:** Swedish Society of Medicine and the Selander Foundation **Study name:** FASTER 1-study and FAST II study **Recruitment:** May 2000 (FAST II), October 2002 (FASTER I) to March 2001 (FAST II), August 2003 (FASTER I) **Number of participants eligible (enrolled):** 495 (360)	**Inclusion criteria:** Chest pain with ≥ 15-minute duration within the last 24 hours (FAST II-study), or the last 8 hours (FASTER I-study). Analysis restricted to patients with symptom onset < 8 hours **Exclusion criteria:** ST segment elevation on the admission 12-lead ECG, leading to immediate reperfusion therapy or its consideration was used as exclusion criterion **Patient category:** NSTEMI	**Median age (IQR), years:** 67 (58–76) **Male (%):** 66 **Previous AMI (%):** 38 **Previous revascularisation (%):** 18 **Diabetes (%):** 18 **Smoking (%):** 18 **Hypertension (%):** 43 **Dyslipidaemia (%):** 38 **Delay < 4 hours (%)**: 40	Roche
Freund (2011)[49,71] **Country:** France **Funding:** Assay kits for the study were provided by the manufacturers (Roche) **Recruitment:** August 2005 to January 2007 **No. of participants:** 317	**Inclusion criteria:** Consecutive adults (> 18 years) presenting to the ED with chest pain suggestive of ACS (onset or peak within the previous 6 hours) **Exclusion criteria:** Patients with acute kidney failure requiring dialysis were excluded **Patient category:** Mixed (13 were STEMI and 32 NSTEMI)	**Mean (SD):** 57 (17) **Male (%):** 65 **Previous CAD (%):** 26 **Previous family history (%):** 32 **Diabetes (%):** 14 **Smoking (%):** 40 **Hypertension (%):** **Dyslipidaemia (%):** 36	Roche
Hoeller (2011)[39,43,45,47,52,53,56,63,65,66,72] **Countries:** Switzerland, Spain, USA and Germany **Funding:** Swiss National Science Foundation, Swiss Heart Foundation, Department of Internal Medicine of the University Hospital Basel, Roche, Siemens, Abbott, Brahms, nanosphere, and 8sense **Study name:** APACE trial (NCT00470587) **Recruitment:** April 2006 to August 2011 **Number of participants:** 2245	**Inclusion criteria:** Consecutive adults presenting to the ED with symptoms suggestive of AMI (e.g. acute chest pain, angina pectoris at rest, other thoracic sensations) within an onset or peak within the last 12 hours **Exclusion criteria:** Terminal kidney failure requiring dialysis **Patient category:** Mixed	**Median age (IQR), years:** 62 (50–75) **Male (%):** 69 **Previous AMI (%):** 24 **Previous CAD (%):** 34 **Previous family history (%):** 43 **Previous revascularisation (%):** 24 **Diabetes (%):** 18 **Smoking (%):** 61 **Hypertension (%):** 64 **Dyslipidaemia (%):** 45 **Median BMI (IQR), kg/m²:** 27 (24–30) **Presenting < 3 hours from symptom onset (%):** 24	Roche, Abbott, Beckman Coulter

Study details	Selection criteria	Participant details	Test manufacturer
Keller (2011)[48,69] **Country:** Germany **Funding:** Abbott Diagnostics provided study funding **Recruitment:** January 2007 to December 2008 **Number of participants:** 1818	**Inclusion criteria:** Consecutive adults (18–85 years) presenting to three chest pain units with chest pain suggestive of ACS **Exclusion criteria:** Major surgery or trauma within the previous 4 weeks; pregnancy; intravenous drug abuse; anaemia (haemoglobin < 10 g/dl) **Patient category:** Mixed	**Mean age (SD), years:** 61 (14) **Male (%):** 66 **Previous CAD (%):** 36 **Previous family history (%):** 32 **Diabetes (%):** 16 **Smoking (%):** 24 **Hypertension (%):** 74 **Dyslipidaemia (%):** 73 **Mean BMI (SD), kg/m²:** 28 (5)	Abbott
Kurz (2011)[55] **Country:** Germany **Funding:** Investigators were supported by Roche diagnostics and assay kits were also provided by the manufacturer **Recruitment:** May 2008 to December 2008 **Number of participants:** 94	**Inclusion criteria:** Consecutive patients admitted to a chest pain unit with symptoms suggestive of ACS **Exclusion criteria:** ST segment elevation; severe kidney dysfunction (glomerular filtration rate < 60 ml/minute/1.73 m²); patients undergoing percutaneous coronary intervention during follow-up sampling **Patient category:** NSTEMI	**Mean age (SD), years:** 66 (11) **Male (%):** 71 **Previous AMI (%):** 37 **Previous CAD (%):** 50 **Previous family history (%):** 32 **Previous revascularisation (%):** 17 **Diabetes (%):** 31 **Smoking (%):** 22 **Hypertension (%):** 78 **Dyslipidaemia (%):** 65 **Median symptom onset (IQR, minutes):** 358 (152–929) **BMI (95% CI/range/IQR):** 28 (4)	Roche
Lippi (2012)[73] **Country:** Italy **Funding:** NR **Recruitment:** NR **Conference abstract only** **Number of participants:** 57	**Inclusion criteria:** Consecutive patients presenting to the ED with chest pain, within 3 hours of the onset of pain **Exclusion criteria:** None reported **Patient category:** Mixed	No participant details reported	Beckman

Study details	Selection criteria	Participant details	Test manufacturer
Melki (2011)[51,61] **Country:** Sweden **Funding:** Partially supported by a grant from Roche Diagnostics, who also provided reagents. Also supported by the Swedish Heart and Lung Foundation and National Board of Health and Welfare **Recruitment:** August 2006 to January 2008 **Number of participants:** 233	**Inclusion criteria:** Patients admitted to a coronary care unit with chest pain or other symptoms suggestive of ACS within 12 hours of admission **Exclusion criteria:** Patients with persistent ST segment elevation **Patient category:** NSTEMI	**Median age (IQR), years:** 65 (55–76) **Male (%):** 67 **Previous AMI (%):** 30 **Previous revascularisation (%):** 21 **Diabetes (%):** 23 **Smoking (%):** 17 **Hypertension (%):** 50 **Mean symptom onset (95% CI/range/IQR, hours):** 5 (3–8)	Roche
Parsonage (2013)[58] **Country:** Australia **Funding:** NR **Recruitment:** NR **Conference abstract only** **Number of participants:** 737	**Inclusion criteria:** Patients with symptoms of possible ACS **Exclusion criteria:** None reported **Patient category:** Mixed	**Mean age (IQR):** 54 (44–65) **Male (%):** 60	Abbott, Roche
Saenger (2010)[70] **Country:** USA **Funding:** Two authors declared individual funding from manufacturers (one from Roche diagnostics and one from Beckman Coulter and Abbott) **Recruitment:** NR **Conference abstract only** **Number of participants:** 288	**Inclusion criteria:** Patients presenting to the ED with symptoms suggestive of AMI **Exclusion criteria:** None reported **Patient category:** Mixed **Details:** NSTEMI 19%, STEMI 15%	No further participant details reported	Roche

Study details	Selection criteria	Participant details	Test manufacturer
Sanchis (2012)[42] **Country:** Spain **Funding:** Supported by a grant from Roche Diagnostics **Study name:** PITAGORAS study **Recruitment:** NR **Number of participants:** 446	**Inclusion criteria:** Patients presenting to the ED with chest pain of possible coronary origin and onset of pain within the previous 24 hours **Exclusion criteria:** Exclusion criteria: persistent ST segment elevation on ECG; Tn elevation in any of two serial determinations (at arrival and 6–8 hours later); prior diagnosis of ischaemic heart disease by either the finding of significant stenosis in a prior coronary angiogram or previously documented AMI; left bundle branch block or other non-interpretable ECG or inability to performance exercise test; structural heart disease different from ischaemic heart disease; concomitant HF or significant bradyarrhythmia (< 55 beats/minute) or tachyarrhythmia (> 110 beats/minute) at admission **Patient category:** NSTEMI	**Mean age (SD), years:** 60 (12) **Male (%):** 59 **Previous family history (%):** 14 **Diabetes (%):** 20 **Smoking (%):** 25 **Hypertension (%):** 54 **Dyslipidaemia (%):** 46	Roche
Santaló (2013)[40] **Country:** Spain **Funding:** Reagents and logistical support were provided by Roche diagnostics **Study name:** TUSCA study **Recruitment:** NR **Number of participants:** 358	**Inclusion criteria:** Adult (> 18 years) described as presenting with acute coronary syndromes and symptom duration ≥ 5 minutes; population included 174 people with a final diagnosis of non-acute coronary syndromes **Exclusion criteria:** Exclusion criteria: ST segment elevation; new left bundle branch block; pre-admission thrombolytic therapy; defibrillation or cardioversion before sampling; pregnancy; renal failure requiring dialysis; UA within 2 months; coronary artery bypass graft within 3 months **Patient category:** NSTEMI	**Mean age (range), years:** 69 (27–93) **Male (%):** 68 **Previous CAD (%):** 35 **Diabetes (%):** 26 **Hypertension (%):** 62 **Presentation within 3 hours:** 46.2%	Roche

Study details	Selection criteria	Participant details	Test manufacturer
Sebbane (2013)[64] **Country:** France **Funding:** Study funded by the hospital, with assay reagents supplied by the manufacturers **Recruitment:** December 2009 to November 2011 **Number of participants:** 248	**Inclusion criteria:** Adults presenting to the ED with chest pain of recent (within 12 hours of presentation) **Exclusion criteria:** Traumatic causes of chest pain. STEMI was defined by the persistent elevation of the ST segment of at least 1 mm in two contiguous ECG leads or by the presence of a new left bundle branch block with positive cardiac enzyme results. Patients with STEMI were excluded from the analysis for our review **Patient category:** NSTEMI (data also reported for mixed AMI but not extracted)	**Median age (IQR), years:** 61 (48–75) **Male (%):** 63	Roche

NR, not reported; IQR, interquartile range; SD, standard deviation.

Index test and reference standard details

	High-sensitivity Tn details (ng/l)				Reference standard details				
Study details	Manufacturer	LoD	99th centile	CV	Target condition	Time frame	Reference standard	Standard Tn	Observer
Aldous (2012)[41,46,50]	Roche Elecsys hs-cTnT	5	14	< 10% at 13	NSTEMI	NR	ACC[109]	Conventional Tns were measured using Abbott Diagnostics TnI (LoD 10 ng/l, 99th centile 28 ng/l, CV < 10% at 32 ng/l, decision threshold 30 ng/l) *Timing:* On presentation, and at 2 hours and 6–12 hours	Diagnoses on admission and at follow-up were independently adjudicated by one cardiologist, who was blinded to hs-cTnT results
Aldous (2011)[54,62,68]	Roche Elecsys hs-cTnT	5	14	< 10% at 13	AMI	NR	Joint ESC, ACC, AHA and WHF[8]	Conventional Tns were measured using Abbott Diagnostics TnI 2 (LoD 10 ng/l, 99th centile 28 ng/l, CV < 10% at 32 ng/l) Change (rise or fall) in TnI 2, or no change but no clear alternative cause of Tn elevation, were considered indicative of AMI *Timing:* On presentation and at follow-up (6–24 hours)	Final diagnoses were adjudicated independently by cardiologists, blinded to patient history and hs-cTnT

	High-sensitivity Tn details (ng/l)				Reference standard details				
Study details	Manufacturer	LoD	99th centile	CV	Target condition	Time frame	Reference standard	Standard Tn	Observer
Body (2011)[60,67,74]	Roche Elecsys hs-cTnT	NR	14	< 10% at 9	AMI	12 hours	Joint ESC, ACC, AHA and WHF[8]	Rise or fall of cTnT, or both, above the 99th percentile (10 ng/l) in the appropriate clinical context For patients with modest elevations of cTnT (< 0.1 ng/ml) at baseline, an absolute difference of at least 20 ng/l on serial sampling was considered to represent a significant rise, fall, or both based on the analytical performance of the cTnT assay *Timing:* At least 12 hours after the onset of the most significant symptoms	Two independent investigators, who had all clinical, laboratory, and imaging data available for review, but who were blinded to hs-cTnT levels
Christ (2010)[57]	Roche Elecsys hs-cTnT	3	14	< 10% at 13	AMI	NR	Joint ESC, ACC, AHA and WHF[8]	Myocardial necrosis was diagnosed on the basis of a rising and/or falling cTnT pattern > 20% or < 20% compared with the cTnT levels admission) with at least one value above the 99th percentile and an imprecision of < 10% Myocardial necrosis not related to AMI was defined as a typical rise and fall of cTnT levels without clinical evidence of CAD, and cardiac pain without necrosis was defined as a typical patient history and clinical signs of cardiac pain without increased levels of cTnT	Two independent consultants

Study details	High-sensitivity Tn details (ng/l)				Reference standard details				
	Manufacturer	LoD	99th centile	CV	Target condition	Time frame	Reference standard	Standard Tn	Observer
								UA was diagnosed when a patient had normal Tn levels and typical angina at rest or exercise, or a cardiac catheterisation result compatible with the diagnosis cTnT cut-off level of 0.04 µg/l *Timing:* At presentation and about 6 hours at discretion of physician	
Collinson (2013)[19,58,59]	Roche Elecsys hs-cTnT	3	14	< 10% at 13	NSTEMI	NR	Joint ESC, ACC, AHA and WHF[8]	Conventional Tns were measured using one of the following methods: Siemens cTnI Ultra (LoD 6 ng/l, 99th centile 40 ng/l, CV 10% at 30 ng/l) Abbott cTnI (LoD 10 ng/l, 99th centile 12 ng/l, CV 10% at 32 ng/l) Beckman AccuTnI (LoD 10 ng/l, 99th centile 40 ng/l, CV 10% at 60 ng/l) Roche cTnT (LoD 10 ng/l, 99th centile 10 ng/l, CV 10% at 30 ng/l) *Timing:* On presentation and at 10–12 hours	An initial working diagnosis was recorded by the senior ED clinician and reviewed by two independent clinicians; all were blind to hs-cTnT results

	High-sensitivity Tn details (ng/l)				Reference standard details				
Study details	Manufacturer	LoD	99th centile	CV	Target condition	Time frame	Reference standard	Standard Tn	Observer
Cullen (2013)[63]	Abbott ARCHITECT hs-cTnI STAT	1.2	26.2	< 5% at 26.2	MACE	30 days	MACE	NR	Adjudication of all cardiac end points was made by two cardiologists, with consultation of a third cardiologist in case of disagreement
Eggers (2012)[44]	Roche Elecsys hs-cTnT	3	14	< 10% at 13	NSTEMI	NR	Joint ESC, ACC, AHA and WHF[8]	cTnI (Stratus CS: Siemens Healthcare Diagnostics, Deerfield, IL, USA). Non-STEMI defined as: cTnI above the 99th percentile of 0.07 µg/l at least at one measurement together with a ≥ 20% rise and/or fall and an absolute change ≥ 0.05 µg/l within 24 hours To allow for the calculation of relative changes, cTnI was set to 0.02 µg/l (i.e. a concentration below the lowest level of detection) when reported as 0.00 or 0.01 µg/l *Timing:* Eight time points during the first 24 hours following enrolment	NR
Freund (2011)[49,71]	Roche Elecsys hs-cTnT	3	14	< 10% at 14	AMI	30 days	Joint ESC, ACC, AHA and WHF[8]	cTnI (Siemens Healthcare Diagnostica Inc., NewarK, USA or Access analyser Beckman Coulter Inc., Brea, USA). Threshold for Siemens assay 140 ng/l, CV 10% Threshold for Beckman assay 60 ng/l, CV 10% *Timing:* On presentation and at 3–9 hours if needed	Two independent ED physicians, who were blinded to hs-cTnT results. Disagreements were adjudicated by a third ED physician

	High-sensitivity Tn details (ng/l)				Reference standard details				
Study details	Manufacturer	LoD	99th centile	CV	Target condition	Time frame	Reference standard	Standard Tn	Observer
Hoeller (2011) APACE[39,47,52,53,56,65]	Roche Elecsys hs-cTnT	5	14	< 10% at 13	AMI	NR	Joint ESC, ACC, AHA and WHF[8]	Conventional Tns were measured using Roche cTnT fourth generation assay (CV < 10% at 35 ng/l), Beckman Coulter Accu cTnI (CV < 10% at 60 ng/l), or Abbott Axsym cTnI ADV (CV < 10% at 160 ng/l). A positive test was defined as change ≥ 30% of 99th centile or 10% CV level, within 6 to 9 hours *Timing:* On presentation and at 6–9 hours	Final diagnoses were adjudicated by two independent cardiologists blind to hsTnT results. When there was disagreement, a third cardiologist was consulted
APACE[72]		2							
APACE[39,65]	Beckman (pre-commercial assay)	2	9	< 10% at 9	AMI and NSTEMI	30 days			
APACE[63]	Abbott ARCHITECT hs-cTnI STAT	1.2	26.2	< 5% at 26.2	AMI	30 days			
APACE[39]					MACE			NA	Adjudication of all cardiac end points was made by two cardiologists, with consultation of a third cardiologist in case of disagreement
Keller (2011)[48]	Abbott ARCHITECT hs-cTnI STAT	3.4	24–30 for this study population	10% at 5.2	AMI	30 days	Joint ESC, ACC, AHA and WHF[8]	Conventional serial Tn T or I (no further details) *Timing:* On presentation and at 3 and 6 hours	Final diagnosis adjudicated by two independent cardiologists, with disagreements referred to a third cardiologist; all three were blinded to hs-TnI results
Kurz (2011)[55]	Roche Elecsys hs-cTnT	3	13.5	8% at 10	NSTEMI	24 hours	Joint ESC, ACC, AHA and WHF[8]	Fourth generation cTnT (Roche Elecsys, Mannheim, Germany) LoD 10 ng/l, diagnostic threshold 30 ng/l Diagnosis of NSTEMI required elevated cTnT concentration in at least one of the consecutive samples collected within 24 hours of the index event *Timing:* On presentation, at 6 hours and at least one sample between presentation and 6 hours	NR

	High-sensitivity Tn details (ng/l)				Reference standard details				
Study details	Manufacturer	LoD	99th centile	CV	Target condition	Time frame	Reference standard	Standard Tn	Observer
Lippi (2012)[73]	Beckman Coulter prototype hs-cTnI (hs-Accu-TnI)	2.1	8.6	NR	AMI	NR	AMI (unclear method)	NR	NR
Melki (2011)[51,61]	Roche Elecsys hs-cTnT	2	14	< 10% at 13	NSTEMI	NR	Joint ESC, ACC, AHA and WHF[8]	Conventional Tn Roche fourth generation TnT (LoD 10 ng/l, 10% CV at 35 ng/l), or Beckman Coulter Access AccuTnI (LoD 10 ng/l, 99th centile 40 ng/l, CV < 10% at 60 ng/l *Timing:* On presentation and 9 to 12 hours later	Final diagnosis determined by the individual cardiologist, then adjudicated by two independent evaluators; all three were blinded to hs-TnT results
Parsonage (2013)[58]	Abbott ARCHITECT hs-cTnI STAT	NR	26.2	NR	AMI	NR	AMI (unclear method)	NR *Timing:* On admission and > 6 hours after presentation	Final diagnosis was adjudicated by two independent cardiologists
Saenger (2010)[70]	Roche Elecsys hs-cTnT	NR	14	NR	AMI	NR	AMI (unclear method)	NR	NR
Sanchis (2012)[42]	Roche Elecsys hs-cTnT	3	14	< 10% at 14	MACE	30 days	MACE	NR	NR
Santaló (2013)[40]	Roche Elecsys hs-cTnT	NR	14	10% at 9.3	NSTEMI	NR	National Academy of Clinical Biochemistry and International Federation of Clinical Chemistry Committee[101]	Roche cTnT; NSTEMI was defined as cTnT > 10 ng/l and ΔcTnT > 20% *Timing:* 30 minutes after arrival and at 2, 4 and 6–8 hours or until discharge	Final diagnosis was made by an adjudication committee

Study details	High-sensitivity Tn details (ng/l)				Reference standard details				
	Manufacturer	LoD	99th centile	CV	Target condition	Time frame	Reference standard	Standard Tn	Observer
Sebbane (2013)[64]	Roche Elecsys hs-cTnT	5	14	< 10% at 13	NSTEMI	NR	Joint ESC, ACC, AHA and WHF[8]	cTnI measured using the Access2 analyser (Access Immunosystem, Beckman Instruments, France). The LoD was < 10 ng/l and the decision threshold was 40 ng/l *Timing:* Convention cardiac Tn (cTnI) on presentation, 6 hours later and beyond as needed	Two independent ED physicians, blinded to hs-cTnT results

NR, not reported; SD, standard deviation.

Study results

Study details	Tn assay	Timing	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
Aldous (2011)[54]	Roche	On presentation	14	AMI	92	36	18	186	83 (75 to 89)	84 (78 to 88)	5.1 (3.7 to 6.9)	0.2 (0.13 to 0.3)
			5		106	131	4	91	96 (90 to 98)	41 (35 to 48)	1.6 (1.4 to 1.8)	0.1 (0.04 to 0.25)
			13		92	38	18	184	83 (75 to 89)	83 (77 to 87)	4.8 (3.6 to 6.5)	0.2 (0.13 to 0.31)
			15		93	29	17	193	84 (76 to 90)	87 (82 to 91)	6.4 (4.5 to 9)	0.18 (0.12 to 0.28)
Aldous (2012)[41]	Roche	On presentation	14	AMI	74	54	8	249	90 (81 to 95)	82 (77 to 86)	5 (3.9 to 6.4)	0.12 (0.07 to 0.24)
		0–1 hours after presentation	14		77	63	5	240	93 (86 to 97)	79 (74 to 83)	4.5 (3.6 to 5.6)	0.08 (0.04 to 0.19)
		0–2 hours after presentation	14		78	67	4	236	95 (87 to 98)	78 (73 to 82)	4.3 (3.4 to 5.3)	0.07 (0.03 to 0.17)
		On presentation and at 2 hours	14 and no change		78	74	4	229	95 (87 to 98)	75 (70 to 80)	3.9 (3.1 to 4.7)	0.07 (0.03 to 0.18)
			< 14 and Δ20%		49	81	33	222	60 (49 to 70)	73 (68 to 78)	2.2 (1.7 to 2.9)	0.55 (0.42 to 0.72)
			14 and Δ20%		46	23	36	280	56 (45 to 66)	92 (89 to 95)	7.2 (4.7 to 11.2)	0.48 (0.37 to 0.61)
			14 or Δ20%		81	131	1	172	98 (93 to 100)	57 (51 to 62)	2.3 (2 to 2.6)	0.03 (0.01 to 0.16)
Aldous (2012)[46]	Roche	On presentation	14	NSTEMI	181	134	24	600	88 (83 to 92)	82 (79 to 84)	4.8 (4.1 to 5.7)	0.15 (0.1 to 0.21)
		On presentation	5		192	305	13	429	93 (89 to 96)	58 (55 to 62)	2.2 (2 to 2.5)	0.11 (0.07 to 0.19)
		On presentation	3		196	383	9	351	95 (92 to 98)	48 (44 to 51)	1.8 (1.7 to 2)	0.1 (0.05 to 0.18)
		2 hours after presentation	14		189	149	16	585	92 (87 to 95)	80 (77 to 82)	4.5 (3.9 to 5.2)	0.1 (0.06 to 0.16)
			5		196	340	9	394	95 (92 to 98)	54 (50 to 57)	2.1 (1.9 to 2.2)	0.09 (0.05 to 0.16)
			3		201	424	4	310	98 (95 to 99)	42 (39 to 46)	1.7 (1.6 to 1.8)	0.05 (0.02 to 0.13)
Data from: Aldous (2011)[50]		0–2 hours after presentation	Peak 14		189	149	11	590	94 (90 to 97)	80 (77 to 83)	4.7 (4 to 5.4)	0.07 (0.04 to 0.13)
			14 and Δ20%		99	43	101	696	50 (43 to 56)	94 (92 to 96)	8.4 (6.1 to 11.6)	0.54 (0.47 to 0.62)
			14 or Δ20%		195	260	5	479	97 (94 to 99)	65 (61 to 68)	2.8 (2.5 to 3.1)	0.04 (0.02 to 0.1)

Study details	Tn assay	Timing	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
Body (2011)[68]	Roche	On presentation	3	AMI	130	378	0	195	100 (96 to 100)	34 (30 to 38)	1.5 (1.4 to 1.6)	0.01 (0 to 0.18)
		On presentation	14		111	101	19	472	85 (78 to 90)	82 (79 to 85)	4.8 (4 to 5.8)	0.18 (0.12 to 0.27)
		On presentation: symptom onset < 3 hours	3		79	89	0	156	99 (94 to 100)	64 (57 to 69)	2.7 (2.3 to 3.2)	0.01 (0 to 0.16)
		On presentation: symptom onset < 3 hours	14		63	42	13	203	82 (72 to 89)	83 (78 to 87)	4.8 (3.6 to 6.4)	0.21 (0.13 to 0.35)
		On presentation: symptom onset > 3 hours	3		51	221	0	107	99 (91 to 100)	33 (28 to 38)	1.5 (1.4 to 1.6)	0.03 (0 to 0.47)
		On presentation: symptom onset > 3 hours	14		47	59	4	269	91 (81 to 96)	82 (77 to 86)	5.1 (4 to 6.5)	0.11 (0.04 to 0.26)
		On presentation: symptom onset < 6 hours	3		105	253	0	133	100 (96 to 100)	34 (30 to 39)	1.5 (1.4 to 1.6)	0.01 (0 to 0.22)
		On presentation: symptom onset < 6 hours	14		87	66	18	320	83 (74 to 89)	83 (79 to 86)	4.8 (3.8 to 6.1)	0.21 (0.14 to 0.32)
		On presentation: symptom onset > 6 hours	3		25	125	0	62	98 (84 to 100)	33 (27 to 40)	1.5 (1.3 to 1.6)	0.06 (0 to 0.91)
		On presentation: symptom onset > 6 hours	14		24	35	1	152	94 (78 to 99)	81 (75 to 86)	5 (3.7 to 6.8)	0.07 (0.02 to 0.34)

Study details	Tn assay	Timing	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
Christ (2010)[57]	Roche	On presentation	14	AMI	19	45	1	72	93 (74 to 98)	61 (52 to 70)	2.4 (1.9 to 3.1)	0.12 (0.02 to 0.55)
Christ (2010)[57]	Roche	On presentation	14	AMI	20	92	0	25	100 (81 to 100)	22 (15 to 30)	1.25 (1.11 to 1.40)	0.11 (0.01 to 1.74)
Collinson (2013)[19]	Roche	On presentation	14	NSTEMI	53	33	14	733	79 (68 to 87)	96 (94 to 97)	18 (12.6 to 25.7)	0.22 (0.14 to 0.35)
		On presentation and at 1.5 hours	Peak 14	NSTEMI	57	43	11	736	83 (73 to 90)	94 (93 to 96)	14.9 (11 to 20.3)	0.18 (0.1 to 0.3)
Cullen (2013)[63]	Abbott	On presentation and at 2 hours	26.2 on admission and at 2 hours	MACE	227	96	20	1292	92 (88 to 95)	93 (92 to 94)	13.2 (10.9 to 16.1)	0.09 (0.06 to 0.13)
Eggers (2012)[44]	Roche	On presentation	14	NSTEMI	101	59	27	173	79 (71 to 85)	74 (68 to 80)	3.1 (2.4 to 3.9)	0.29 (0.2 to 0.4)
			45.7	NSTEMI	65	11	63	221	51 (42 to 59)	95 (91 to 97)	10.3 (5.7 to 18.5)	0.52 (0.43 to 0.62)
Freund (2011)[49]	Roche	On presentation	14	AMI	42	48	3	224	92 (81 to 97)	82 (77 to 86)	5.2 (4 to 6.8)	0.09 (0.03 to 0.25)
		On presentation: low/moderate pre-test probability			20	36	2	200	89 (70 to 97)	85 (79 to 89)	5.8 (4.2 to 8.1)	0.13 (0.04 to 0.41)
		On presentation: high pre-test probability			22	12	1	24	94 (77 to 99)	66 (50 to 79)	2.8 (1.7 to 4.4)	0.09 (0.02 to 0.45)
Hoeller (2011)[39]	Roche	On presentation	14	AMI	398	363	46	1265	90 (86 to 92)	78 (76 to 80)	4 (3.6 to 4.4)	0.13 (0.1 to 0.18)
		On presentation: symptom onset < 3 hours	14		79	63	28	335	74 (65 to 81)	84 (80 to 87)	4.6 (3.6 to 6)	0.31 (0.23 to 0.43)
		On presentation: symptom onset ≥ 3 hours	14		318	300	18	931	95 (92 to 96)	76 (73 to 78)	3.9 (3.5 to 4.3)	0.07 (0.05 to 0.11)
	Beckman	On presentation	9		209	231	18	693	92 (88 to 95)	75 (72 to 78)	3.7 (3.3 to 4.1)	0.11 (0.07 to 0.17)
	Abbott		26.2		240	93	71	1163	77 (72 to 81)	93 (91 to 94)	10.4 (8.4 to 12.7)	0.25 (0.2 to 0.3)

Study details	Tn assay	Timing	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
Data from: Reichlin (2009)[74]	Roche	On presentation	2		123	512	0	83	100 (97 to 100)	14 (11 to 17)	1.2 (1.1 to 1.2)	0.03 (0.00 to 0.46)
	Abbott		10		116	77	7	518	94 (89 to 98)	87 (84 to 90)	7.3 (5.9 to 9.0)	0.07 (0.03 to 0.13)
Data from: Reiter (2011)[53]	Roche	On presentation: > 70 years only	5		98	305	0	3	99 (95 to 100)	1 (0 to 3)	1 (1 to 1)	0.45 (0.02 to 8.56)
		On presentation: > 70 years only	14		96	157	2	151	97 (92 to 99)	49 (44 to 55)	1.9 (1.7 to 2.1)	0.05 (0.02 to 0.18)
		On presentation: ≤ 70 years	14		54	87	7	533	88 (78 to 94)	86 (83 to 88)	6.2 (5 to 7.7)	0.14 (0.07 to 0.28)
Data from: Potocki (2012)[47]		On presentation: with pre-existing CAD	14		73	142	5	213	93 (85 to 97)	60 (55 to 65)	2.3 (2 to 2.7)	0.12 (0.05 to 0.26)
		On presentation: without pre-existing CAD	14		100	114	6	517	94 (88 to 97)	82 (79 to 85)	5.2 (4.4 to 6.2)	0.07 (0.04 to 0.16)
Data from: Hochholzer (2011)[56]		On presentation	11		129	177	3	454	97 (93 to 99)	72 (68 to 75)	3.5 (3.1 to 3.9)	0.04 (0.01 to 0.1)
		On presentation	11	NSTEMI	90	177	3	454	96 (90 to 99)	72 (68 to 75)	3.4 (3 to 3.9)	0.05 (0.02 to 0.14)
Data from: Irfan (2013)[65]	Beckman	On presentation and at 1 hour	Δ17%		65	202	43	520	60 (51 to 69)	72 (69 to 75)	2.1 (1.8 to 2.6)	0.55 (0.44 to 0.7)
			Δ27%		68	245	40	477	63 (53 to 71)	66 (63 to 69)	1.9 (1.6 to 2.2)	0.56 (0.44 to 0.72)
Data from: Reichlin (2011)[52]	Roche	On presentation and at 2 hours	Δ30%		43	84	24	439	64 (52 to 74)	84 (80 to 87)	4 (3 to 5.2)	0.43 (0.31 to 0.59)
Data from: Cullen (2013)[63]	Abbott		26.2 on admission and at 2 hours	MACE	129	62	27	691	82 (76 to 88)	92 (90 to 93)	10 (7.8 to 12.8)	0.19 (0.14 to 0.27)

Study details	Tn assay	Timing	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
Keller (2011)[48]	Abbott	On presentation	3.4	AMI	282	633	0	345	100 (98 to 100)	35 (32 to 38)	1.5 (1.5 to 1.6)	0.01 (0 to 0.08)
			30	AMI	232	77	50	901	82 (77 to 86)	92 (90 to 94)	10.4 (8.3 to 12.9)	0.19 (0.15 to 0.25)
		3 hours after presentation	3.4	AMI	282	959	0	19	100 (98 to 100)	2 (1 to 3)	1 (1 to 1)	0.09 (0.01 to 1.46)
			30	AMI	277	94	5	884	98 (96 to 99)	90 (88 to 92)	10.2 (8.4 to 12.3)	0.02 (0.01 to 0.05)
		On presentation and at 3 hours	Δ20%	AMI	218	723	64	255	77 (72 to 82)	26 (23 to 29)	1 (1 to 1.1)	0.87 (0.69 to 1.11)
			3.4 on admission and Δ20%	AMI	254	454	54	498	82 (78 to 86)	52 (49 to 55)	1.7 (1.6 to 1.9)	0.34 (0.26 to 0.43)
			30 after 3 hours and Δ20%	AMI	187	34	110	929	63 (57 to 68)	96 (95 to 97)	17.6 (12.5 to 24.7)	0.38 (0.33 to 0.45)
			30 after 3 hours and Δ20% to in patients < 30 ng/l on admission	AMI	52	26	4	869	92 (82 to 97)	97 (96 to 98)	31.1 (21.2 to 45.7)	0.08 (0.03 to 0.2)
Kurz (2011)[55]	Roche	On presentation	9.5	NSTEMI	38	11	8	37	82 (69 to 90)	77 (63 to 86)	3.5 (2.1 to 5.9)	0.24 (0.13 to 0.44)
			14	NSTEMI	16	7	10	24	61 (42 to 77)	77 (60 to 88)	2.6 (1.3 to 5.2)	0.51 (0.3 to 0.85)
		Within 3 hours of presentation	14	NSTEMI	26	7	0	23	98 (84 to 100)	76 (58 to 87)	4.1 (2.2 to 7.6)	0.02 (0 to 0.38)
		On presentation and within 3 hours	14 and Δ20%	NSTEMI	11	27	15	3	43 (26 to 61)	11 (4 to 27)	0.5 (0.3 to 0.8)	5.08 (1.8 to 14.37)
Lippi (2012)[73]	Beckman	On presentation	18	AMI	9	17	0	31	95 (66 to 99)	64 (50 to 76)	2.7 (1.8 to 4)	0.08 (0.01 to 1.17)
Melki (2011)[51]	Roche	On presentation	14	NSTEMI	112	21	2	98	98 (93 to 99)	82 (74 to 88)	5.5 (3.7 to 8)	0.03 (0.01 to 0.09)
		2 hours after presentation	14	NSTEMI	114	25	0	94	100 (96 to 100)	79 (71 to 85)	4.7 (3.3 to 6.6)	0.01 (0 to 0.09)

Study details	Tn assay	Timing	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
Parsonage (2013)[58]	Abbott	On presentation	26.2	AMI	45	34	6	652	88 (76 to 94)	95 (93 to 96)	17.4 (12.4 to 24.5)	0.13 (0.06 to 0.27)
		On presentation and at 2 hours	26.2 peak	AMI	47	48	4	638	91 (81 to 96)	93 (91 to 95)	12.9 (9.7 to 17.2)	0.09 (0.04 to 0.23)
	Roche	On presentation	14	AMI	44	75	7	611	86 (74 to 93)	89 (86 to 91)	7.8 (6.1 to 9.9)	0.16 (0.08 to 0.31)
		On presentation and at 2 hours	14 peak	AMI	48	82	3	604	93 (83 to 98)	88 (85 to 90)	7.8 (6.3 to 9.6)	0.08 (0.03 to 0.21)
Saenger (2010)[70]	Roche	On presentation	14	AMI	92	38	6	152	93 (87 to 97)	80 (74 to 85)	4.6 (3.5 to 6.2)	0.08 (0.04 to 0.17)
		On presentation and at 3 hours	Δ 8	AMI	94	9	4	181	95 (89 to 98)	95 (91 to 97)	19.2 (10.3 to 35.7)	0.05 (0.02 to 0.12)
Sanchis (2012)[42]	Roche	On presentation	3	MACE	53	207	9	177	85 (74 to 92)	46 (41 to 51)	1.6 (1.4 to 1.8)	0.33 (0.18 to 0.59)
		On presentation and 6–8 hours	3	MACE	57	234	5	150	91 (82 to 96)	39 (34 to 44)	1.5 (1.3 to 1.7)	0.22 (0.1 to 0.5)
			14	MACE	21	42	41	342	34 (24 to 46)	89 (85 to 92)	3.1 (2 to 4.8)	0.74 (0.62 to 0.89)
Santaló (2013)[40]	Roche	On presentation	14	NSTEMI	71	80	8	199	89 (81 to 94)	71 (66 to 76)	3.1 (2.5 to 3.8)	0.15 (0.08 to 0.28)
		On presentation and at 2–4 and 6–8 hours or until discharge	Δ 20%	NSTEMI	79	94	0	185	99 (94 to 100)	66 (61 to 72)	2.9 (2.5 to 3.5)	0.01 (0 to 0.15)
Sebbane (2013)[64]	Roche	On presentation, or sample taken during pre-hospital management	14	NSTEMI	19	25	6	142	75 (56 to 88)	85 (79 to 89)	4.9 (3.2 to 7.5)	0.29 (0.15 to 0.58)
			18	NSTEMI	19	17	6	150	75 (56 to 88)	90 (84 to 93)	7.2 (4.4 to 11.8)	0.28 (0.14 to 0.54)

Appendix 3 QUADAS-2 assessments

Study: Aldous (2011)[54]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Consecutive adults presenting to the ED with chest pain were eligible for inclusion	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Unselected chest pain population AMI diagnoses may have included both NSTEMI and STEMI	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT on admission and after 6 hours. Data reported for admission, for four thresholds No details of interpretation reported. One threshold was derived from ROC analysis; primary analysis based on 99th centile	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard diagnosis of AMI based on joint ECS and ACC criteria and included serial conventional cTnI (10- to 12-hour time point not specified) Determination of diagnosis was made blind to hs-TnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
Participants for whom stored samples were not available at both time points were excluded	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Study: Aldous (2012)[46]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Patients presenting to the ED between 05.30 and 20.00 hours, and with chest pain	
Was a consecutive or random sample of patients enrolled?	No
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: High**
B. APPLICABILITY	
Patients with ST segment elevation excluded	
Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT Data reported for multiple thresholds based on predetermined properties of the assay Frozen samples used, unclear whether interpretation of index test was blind to reference standard	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard final diagnosis of AMI, based on ACC criteria and including the results of serial conventional cTnI (10- to 12-hour time point not specified), but blinded to hs-TnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Body (2011)[67]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Prospective enrolment of patients; unclear if consecutive	
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Mixed chest pain	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT. Threshold 99th percentile cut point and LoD. Blinding not reported; objective test interpreted prior to reference standard so unlikely to have been influenced by knowledge of reference standard	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Thorgeson criteria; time point not specified. Clinicians were blinded to hs-Tn	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
301 patients were excluded prior to enrolment; all patients enrolled included in 2 × 2 table	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Christ (2010)[57]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Retrospective analysis of consecutive patients presenting to ED with chest pain	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Patients with general chest pain symptoms, includes participants with a final diagnosis of STEMI	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT. Threshold 99th percentile cut point. Blinding not reported; retrospective analysis and so disease status may have been known when interpreting results. However, objective test and so unlikely to have been influenced by knowledge of disease state	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Joint ESC and ACC criteria; time point not specified. Unclear whether clinicians were blinded to hs-Tn. A second consensus diagnosis incorporating hs-Tn was also made and so clinicians may have been aware of the result for the first consensus diagnosis based only on standard Tn	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
No dropouts reported, all included patients accounted for in flow diagram and numbers suggest that Tn results were available for all	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Collinson (2013)[19]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Participants with chest pain and suspected AMI; study uses subgroup of one arm of an RCT. Patients at high risk of NSTEMI excluded	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Chest pain patients excluding those with diagnostic ECG changes	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT on admission and at 90 minutes Reference standard (final diagnosis) determined after hs-TnT Threshold based on assay characteristics including 99th centile	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard diagnosis of AMI based on joint ESC and ACC criteria and included serial conventional cTnT or cTnI (10- to 12-hour time point specified) Determination of diagnosis was made blind to hs-TnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
1125 enrolled, 25 no samples collected, 250 samples taken but study samples not collected	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Study: Cullen (2013)[63]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Consecutively recruited adults presenting to the ED with cardiac symptoms	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Unselected chest pain population AMI diagnoses may have included both NSTEMI and STEMI	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Abbott ARCHITECT hs-STAT TnI; threshold was 99th centile Frozen samples were used, but laboratory technicians were blinded to patient data	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
30-day MACE, adjudicated blind to index tests, but with access to clinical records, ECG and conventional Tn results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
No patients were lost to 30-day follow-up. Procedure for adjudication of 30-day MACE was the same in all cases, but investigations undergone by individual patients varied	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Eggers (2012)[44]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Unclear whether consecutive or random patients were enrolled.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Non-STEMI patients with chest pain presenting to coronary care/chest pain unit	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT. Threshold 99th percentile cut point and 95% specificity value. Blinding not reported; objective test interpreted prior to reference standard so unlikely to have been influenced by knowledge of reference standard	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Joint ESC and ACC criteria; time point not specified. Unclear whether clinicians were blinded to high-sensitivity troponin. A second consensus diagnosis	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
Only 360 patients out of 495 who fulfilled inclusion criteria had all biochemical tests performed and were included in the analysis; reasons for not performing tests were not reported	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Study: Freund (2011)[49]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Consecutive adults presenting to the ED with chest pain (onset or peak within previous 6 hours). Patients with acute kidney failure requiring dialysis were excluded	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Unselected ED chest pain population, includes participants with a final diagnosis of STEMI; data also presented for subgroups with low-moderate and with high pre-test probability	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT on admission and at 3–9 hours if available. Reference standard (final diagnosis) adjudicated by two independent physicians after acute episode. Threshold was 99th centile	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard final diagnosis, based on joint ESC and ACC criteria and included conventional cTnI on admission and at 3–9 hours if needed (10- to 12-hour time point not specified). Clinicians adjudicating final diagnosis were blind to hs-TnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Hoeller (2013)[39]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Patients presenting to the ED with symptoms suggestive of AMI. Consecutive patients with hs-TnT measurements available were included	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Unselected chest pain population AMI diagnoses may have included both NSTEMI and STEMI	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche hs-TnT, Beckman Coulter Hs-AccuTnI and Abbott ARCHITECT hs-TnI on admission Reference standard probably made later than admission; 99th centiles for assays used as diagnostic thresholds (some publications also reported data for ROC-derived thresholds)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard final diagnosis of AMI, ESC criteria and included cTn assays (0 and 6 hours). Unclear whether those adjudicating final diagnosis were blind to hs-TnI/hs-TnT results in all cases, some publications reported blinding	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/no
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
2245 participants were included in the trial, 2072 were included in the hs-TnT analysis, 1151 were included in the hs-TnI (Beckman) analysis, and 1567 were included in the hs-TnI (Abbott) analysis Most exclusions were because hsTn measurements were not available	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Study: Keller (2011)[48]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Consecutive patients presenting to chest pain units	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
General chest pain populations, some participants had a final diagnosis of STEMI	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Abbott Architect STAT hs-TnI, on admission and at 3 hours. Reference standard (final diagnosis) was adjudicated after hs-TnI testing. Thresholds based on test properties, appeared to be prespecified	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard diagnosis of AMI based on joint ESC and ACC criteria and included serial conventional cTnT (10- to 12-hour time point not specified) Determination of diagnosis was made blind to hs-TnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
None of the analyses included all study participants (558 or 867 participants missing)	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Study: Kurz (2011)[55]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Consecutive patients admitted to a chest pain unit. 206 Patients not included owing to 'technical reasons' (not fully defined, e.g. venepuncture not possible)	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Appears to be an unselected chest pain population, STEMI excluded. Second publication[110] is for a retrospectively selected subgroup of participants with a diagnosis of NSTEMI or UA. Patients were admitted to chest pain units	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT, data reported for admission, 3- and 6-hour samples (6-hour data not extracted) Reference standard Tn testing occurred after hs-TnT. Threshold was prespecified for data extracted from Giannitsis *et al.*,[110] but not from Kurz *et al.*[55] (low risk of bias for Giannitsis *et al.*[110] data)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard diagnosis of AMI based on joint ESC and ACC criteria and included serial conventional cTnT (10- to 12-hour time point not specified) Unclear whether determination of diagnosis was made blind to hs-TnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Lippi (2012)[73]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Consecutive patients presenting to the ED with chest pain of recent onset (< 3 hours) No exclusion criteria reported	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Unselected chest pain population AMI diagnoses may have included both NSTEMI and STEMI	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Beckman Coulter HS-AccuTnI on admission. Reference standard final diagnosis (AMI); probably made later than admission hs-TnI. Threshold derived from ROC analysis	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: High**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard final diagnosis of AMI, criteria for diagnosis not reported Unclear whether those adjudicating final diagnosis were blind to hs-TnI	
Is the reference standard likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
No withdrawals reported	
Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Unclear**

Study: Melki (2011)[51]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Recruitment described as 'consecutive except for temporary interruptions of the study due to high work load in the coronary care unit'	
Was a consecutive or random sample of patients enrolled?	No
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: High**
B. APPLICABILITY	
Chest pain patients admitted to chest pain unit, excluding ST segment elevation	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT on admission and at 2 hours. Reference standard (final diagnosis) determined after hs-TnT testing. Threshold based on assay characteristics, appears predetermined	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard diagnosis of AMI based on joint ESC and ACC criteria and included serial conventional cTnT or cTnI (9- to 12-hour time point specified) Determination of diagnosis was made blind to hs-TnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Parsonage (2013)[58]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Prospective studies; no further details on recruitment	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Unselected chest pain population AMI diagnoses may have included both NSTEMI and STEMI	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT and Abbott ARCHITECT hs-STAT TnI. Threshold was 99th centile Index test occurred before adjudication of final diagnosis	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard diagnosis of AMI (criteria unclear) and included serial conventional cTnI (10- to 12-hour time point not specified). Determination of diagnosis was made blind to hs-TnT and hs-TnI results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
Patients appear to be missing from the analyses, as 2 × 2 data (derived from reported sensitivity and specificity estimates and total number of AMI) do not match reported number of test positives	
Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Unclear**

Study: Saenger (2010)[70]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
No details on how patients were selected. No exclusion criteria reported	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
No exclusion criteria reported, reference standard was AMI (diagnosis method not specified),diagnoses included STEMI	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT on admission and after 3 hours. Data reported for admission and 0–3 hours. No details of interpretation reported. Threshold for Δ value derived from ROC analysis; 99th centile also used	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Reference standard diagnosis of AMI (no details reported)	
Is the reference standard likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
No withdrawals reported	
Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Unclear**

Study: Sanchis (2012)[42]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Patients excluded owing to Tn elevation in any of two serial determinations (at arrival and 6–8 hours later) and prior diagnosis of ischaemic heart disease. No details on how patients were selected for the study	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: High**
B. APPLICABILITY	
Selected low-risk population	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT on admission and at 6–8 hours (data reported for admission and peak values). Reference standard (30-day composite) occurred after testing. Thresholds were reported as prespecified	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Composite 30-day end point of AMI, death and revascularisation Not clear whether those adjudicating AMI were aware of hs-TnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
All participants appeared to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Santalo (2013)[40]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Consecutive adult patients presenting to the ED	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Appears to be an unselected ED chest pain population	
Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT on admission and at 2, 4 and 6–8 hours or until discharge (data reported for admission and Δ values). Unclear whether hs-TnT interpreted blind to cTnT	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Final diagnosis adjudicated by committee, based on Roche cTnT at admission and 2, 4 and 6–8 hours or until discharge (10- to 12-hour time point not specified). NSTEMI defined as cTnT > 10 ng/l and ΔcTnT > 20%; also 99th centile. Unclear whether adjudicators were blinded to hs-TnT	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Unclear**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Sebbane (2013)[62]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
No details on how patients were selected for inclusion	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Unselected cohort of adult patients presenting with chest pain of recent onset (within 12 hours)	
Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Roche Elecsys hs-TnT on admission or from sample taken during pre-hospital management. Final diagnosis adjudicated 1 month after acute episode. Optimal diagnostic thresholds were determined using within-study ROC analyses; 99th centile also reported	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Diagnosis determined by two independent ED physicians, based on joint ESC and ACC criteria. Reference standard included cTnI taken on admission, at 6 hours and beyond, as needed (10- to 12-hour time point not specified). Physicians had access to serial cTnI results, but were blinded to hs-TnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
54 patients were excluded from the analyses because of missing data, including lack of copeptin, hs-cTnT, and cTnI measurements	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Appendix 4 Table of excluded studies with rationale

To be included in the review, studies had to fulfil the following criteria:

Population Adults (≥ 18 years) presenting with acute 'pain, discomfort or pressure in the chest, epigastrium, neck, jaw, or upper limb without an apparent non-cardiac source' attributable to a suspected, but not proven, AMI or ACS.

Setting Secondary or tertiary care.

Index test Abbott ARCHITECT (STAT hs-cTnI); Beckman Coulter Access and Unicel DxI (accuTnI+ 3); Roche Elecsys (cTnT-hs or cTnT-hs STAT); results available within 3 hours.

Reference standard Universal definition of AMI, including measurement of Tn T or I (using any method not defined as a hs-cTn test) on presentation and 10–12 hours after the onset of symptoms in ≥ 80% of the population or occurrence of MACE (any definition used in identified studies) during 30-day follow-up.

Outcome Sufficient data to construct 2 × 2 table of test performance.

The table below summarises studies that were screened for inclusion, based on full-text publication, but which did not fulfil one or more of the above criteria. Studies were assessed sequentially against criteria; as soon as a study had failed, based on one of the criteria, it was not assessed against subsequent criteria. The table shows which of the criteria each study fulfilled ('Yes') and on which item it failed ('No').

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome
Ahmed (2013)[111]	Yes	Yes	Yes	Yes	No	
Aldous (2010)[112]	Yes	Yes	Yes	Yes	Unclear	No
Aldous (2010)[113]	Yes	Yes	Yes	Yes	Unclear	No
Aldous (2012)[114]	No					
Aldous (2010)[115]	Yes	Yes	Yes	Unclear	No	
Aldous (2012)[116]	Yes	Yes	Yes	Unclear	Yes	No
Aldous (2012)[117]	Yes	Yes	Yes	No		
Aldous (2012)[118]	No					
Aldous (2012)[54]	No					
Alexandra (2013)[119]	Yes	Yes	Yes	No		
Arenja (2010)[120]	Yes	Yes	Yes	Yes	No	
Bahrmann (2012)[121]	Yes	No				
Bahrmann (2013)[122]	Yes	No				
Bahrmann (2013)[123]	Yes	No				
Bahrmann (2012)[124]	Yes	Yes	Yes	Yes	No	
Balmelli (2013)[125]	Yes	Yes	Yes	Yes	Unclear	No
Balmelli (2011)[126]	Yes	Yes	Yes	Yes	Unclear	No
Beyrau (2009)[127]	Yes	No				

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome
Bhardwaj (2011)[128]	Yes	Yes	Yes	No		
Bhardwaj (2011)[129]	Yes	Yes	Yes	No		
Biasillo (2010)[130]	Yes	Yes	Yes	Unclear	No	
Biasucci (2010)[131]	Yes	Yes	Yes	Yes	No	
Biasucci (2010)[132]	Yes	Yes	Yes	Yes	No	
Biasucci (2010)[133]	Yes	Yes	Yes	Yes	No	
Biasucci (2010)[134]	Yes	Yes	Yes	Yes	No	
Biasucci (2011)[135]	Yes	Yes	Yes	Yes	No	
Biener (2013)[136]	Yes	Unclear	Yes	Unclear	Unclear	No
Biener (2012)[137]	Yes	Yes	Yes	Unclear	Unclear	No
Biener (2013)[138]	Yes	Yes	Yes	No		
Biosite (2006)[139]	Yes	Yes	Yes	No		
Body (2012)[140]	Yes	Yes	Yes	Unclear	Unclear	No
Body (2012)[141]	Yes	Yes	Yes	Yes	Yes	No
Body (2012)[142]	No					
Braga (2011)[143]	Yes	Yes	Yes	Yes	Yes	No
Braga (2011)[144]	Yes	Yes	Yes	Yes	Yes	No
Bronze (2012)[145]	Yes	Yes	Yes	Yes	No	
Brown (2007)[146]	Yes	Yes	Yes	No		
Buccelletti (2012)[147]	Yes	Yes	Yes	Yes	No	
Buhl (2011)[148]	Yes	No				
Cardillo (2012)[149]	Yes	Yes	Yes	Yes	Yes	No
Carmo (2013)[150]	No					
Ceriani (2012)[151]	No					
Charpentier (2011)[152]	Yes	Yes	Yes	No		
Chenevier-Gobeaux (2013)[153]	No					
Collinson (2012)[154]	Yes	Yes	Yes	No		
Collinson (2012)[155]	Yes	Yes	Yes	No		
Collinson (2012)[156]	Yes	Yes	Yes	No		
Collinson (2006)[157]	Yes	Yes	Yes	No		
Collinson (2010)[158]	Yes	Yes	Yes	No		
Costabel (2013)[159]	No					
Cullen (2011)[160]	Yes	Yes	Yes	No		
Dawson (2013)[161]	Yes	No				
Diercks (2012)[162]	Yes	Yes	Yes	No		
Drexler (2011)[163]	Yes	Yes	Yes	Unclear	Unclear	No
Engel (2007)[164]	Yes	Yes	Yes	No		
Escabi-Mendoza (2010)[165]	Yes	Yes	Yes	No		
Figiel (2008)[166]	Yes	No				

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome
Fitzgerald (2011)[79]	Yes	Yes	Yes	No		
Freund (2011)[167]	Yes	Yes	Yes	Unclear	Unclear	No
Freund (2011)[168]	Yes	Yes	Yes	Unclear	Unclear	No
Giannitsis (2010)[110]	Yes	No				
Giannitsis (2011)[169]	Yes	Yes	Yes	Unclear	Unclear	No
Giavarina (2012)[170]	No					
Giavarina (2011)[171]	Yes	Yes	Yes	No		
Gimenez (2012)[172]	Yes	Yes	Yes	No		
Gimenez (2012)[173]	Yes	Yes	Yes	No		
Goodacre (2011)[80]	Yes	Yes	Yes	No		
Goodacre (2013)[7]	No					
Goodacre (2011)[87]	Yes	Yes	Yes	No		
Gustapane (2012)[174]	Yes	Yes	Yes	Unclear	No	
Gustapane (2012)[175]	Yes	Yes	Yes	Unclear	No	
Haaf (2011)[176]	Yes	Yes	Yes	Unclear	Unclear	No
Haaf (2011)[177]	Yes	Yes	Yes	Unclear	Unclear	No
Haaf (2013)[178]	No					
Haaf (2012)[179]	Yes	Yes	Yes	Yes	No	
Haaf (2012)[180]	Yes	Yes	Yes	Yes	No	
Haltern (2010)[181]	Yes	Yes	Yes	No		
Heinisch (2010)[182]	Yes	Yes	Yes	Unclear	Unclear	No
Hochholzer (2011)[183]	Yes	Yes	Yes	Yes	No	
Hochholzer (2010)[184]	Yes	Yes	Yes	Yes	No	
Hoeller (2012)[185]	Yes	Yes	Yes	Yes	No	
Hoeller (2012)[186]	Yes	Yes	Yes	Yes	No	
Ilva (2009)[187]	Yes	Yes	No			
Inoue (2011)[188]	Yes	Yes	Yes	Yes	No	
Irfan (2011)[189]	Yes	Yes	Yes	Unclear	Unclear	No
Irfan (2011)[190]	Yes	Yes	Yes	Unclear	No	
Irfan (2013)[191]	Yes	Yes	Yes	Yes	Unclear	No
Irfan (2013)[192]	Yes	Yes	Yes	Yes	Unclear	No
Jairam (2011)[193]	Yes	No				
Januzzi (2010)[194]	Yes	Yes	Yes	No		
Januzzi (2009)[195]	Yes	Yes	Yes	Yes	No	
Januzzi (2013)[196]	Yes	Yes	Yes	No		
Jia (2009)[197]	Yes	Yes	Yes	No		
Kagawa (2013)[198]	Yes	Yes	Yes	No		
Karakas (2011)[199]	Yes	Yes	Yes	Yes	No	
Kavsak (2012)[200]	Yes	Yes	Yes	Unclear	Unclear	No

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome
Kavsak (2007)[201]	Yes	Yes	Yes	No		
Kavsak (2013)[202]	Yes	Yes	Yes	Unclear	No	
Kavsak (2005)[203]	Yes	Yes	Yes	No		
Kavsak (2012)[204]	Yes	Yes	Yes	Yes	Unclear	No
Kavsak (2008)[205]	Yes	No				
Kavsak (2011)[206]	Yes	Yes	Yes	Yes	No	
Kavsak (2010)[207]	Yes	Yes	Yes	Yes	Yes	No
Keene (2012)[208]	Yes	Yes	Yes	Yes	No	
Keller (2011)[209]	Yes	Yes	Yes	Yes	Unclear	No
Keller (2011)[210]	Yes	Yes	Yes	Yes	Unclear	No
Keller (2009)[211]	Yes	Yes	Yes	No		
Keller (2010)[212]	Yes	Yes	Yes	No		
Keller (2009)[213]	Yes	Yes	Yes	No		
Kelly (2011)[214]	Yes	Yes	Yes	No		
Khan (2011)[215]	Yes	Yes	Yes	Yes	No	
Khoo (2008)[216]	Yes	Unclear	Yes	No		
Kitamura (2012)[217]	Yes	Yes	Yes	No		
Kobayashi (2011)[218]	Yes	Yes	Yes	Unclear	No	
Kobayashi (2011)[219]	Yes	Yes	Yes	Yes	No	
Koenig (2008)[220]	Yes	Yes	Yes	Yes	No	
Lacnak (2007)[221]	Yes	Yes	Yes	Unclear	No	
Lee (2011)[222]	Yes	Yes	Yes	Unclear	No	
Lindahl (2009)[223]	Yes	No				
Lippi (2013)[224]	No					
Lippi (2012)[225]	No					
Lippi (2013)[226]	No					
Lotze (2011)[227]	Yes	Yes	Yes	No		
Lotze (2011)[228]	Yes	Yes	Yes	Yes	No	
Macrae (2006)[229]	Yes	Yes	Yes	No		
Mair (2011)[230]	Yes	No				
Mair (2011)[231]	Yes	No				
Matsui (2011)[232]	Yes	Yes	Yes	Unclear	Unclear	No
Mazhar (2011)[233]	Yes	Yes	Yes	Unclear	No	
Melanson (2008)[234]	Yes	Yes	Yes	No		
Melki (2011)[235]	Yes	Yes	Yes	Yes	No	
Melki (2011)[236]	Yes	Yes	Yes	No		
Menhofer (2013)[237]	Yes	No				
Meune (2011)[238]	Yes	Yes	Yes	Yes	Yes	No
Meune (2011)[108]	Yes	Yes	Yes	Yes	Yes	No

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome
Meune (2013)[239]	Yes	Yes	Yes	Yes	No	
Meune (2011)[240]	Yes	Yes	Yes	Yes	No	
Mikkel (2013)[241]	Yes	Yes	Yes	Yes	Unclear	No
Mikkel (2013)[242]	Yes	Yes	Yes	No		
Mikkel (2013)[243]	Yes	Yes	Yes	No		
Mills (2010)[244]	Yes	Yes	Yes	Unclear	No	
Mills (2010)[245]	Yes	Yes	Yes	Unclear	No	
Mills (2012)[246]	Yes	Yes	Yes	Yes	No	
Mingels (2012)[247]	Yes	No				
Moehring (2012)[248]	Yes	Yes	Yes	Yes	No	
Moehring (2012)[249]	Yes	Yes	Yes	Yes	Unclear	No
Montagnana (2012)[250]	Yes	Yes	Yes	Yes	Yes	No
Morrow (2009)[251]	No					
Nagurney (2005)[252]	Yes	Yes	Yes	No		
Nanosphere (2010)[253]	Yes	Yes	Yes	Unclear	Yes	No
Naroo (2009)[254]	Yes	Yes	Yes	No		
Ngan (2010)[255]	Yes	Yes	Yes	Yes	Yes	No
Noad (2010)[256]	Yes	Yes	Yes	Unclear	Unclear	No
Normann (2012)[257]	Yes	Yes	Yes	Yes	No	
Nusier (2006)[258]	Yes	Yes	Yes	No		
Olivieri (2012)[259]	Yes	Yes	Yes	No		
Orsborne (2012)[260]	No					
Paoloni (2010)[261]	Yes	Yes	Yes	Unclear	No	
Perego (2011)[262]	Yes					
Plebani (2009)[263]	Yes	Yes	Yes	No		
Ploner (2011)[264]	Yes	No	No			
Popp (2010)[265]	Yes	Yes	Yes	Yes	No	
Potocki (2011)[266]	Yes	Yes	Yes	No		
Pracon (2012)[267]	Yes	Yes	Yes	No		
Rajdl (2011)[268]	Yes	Yes	Yes	Yes	Unclear	No
Ray (2011)[269]	Yes	Yes	Yes	Unclear	Unclear	No
Reichlin (2012)[270]	No					
Reichlin (2011)[271]	Yes	Yes	Yes	Unclear	Unclear	No
Reichlin (2012)[272]	Yes	Yes	Yes	Yes	No	
Reichlin (2010)[273]	Yes	Yes	Yes	Unclear	No	
Reichlin (2010)[274]	Yes	Yes	Yes	Unclear	No	
Reichlin (2012)[275]	Yes	Yes	Yes	Yes	No	
Rubini Gimenez (2012)[276]	Yes	Yes	Yes	Yes	Unclear	No
Rudolph (2011)[277]	Yes	Yes	Yes	Unclear	Unclear	No

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome
Rudolph (2011)[278]	Yes	Yes	Yes	Unclear	Unclear	No
Rudolph (2012)[279]	Yes	Yes	Yes	No		
Samaraie (2010)[280]	Yes	Yes	Yes	Unclear	No	
Scharnhorst (2011)[281]	Yes	Yes	Yes	No		
Schaub (2012)[282]	Yes	Yes	Yes	Yes	Yes	No
Schoos (2013)[283]	Yes	Yes	Yes	Yes	Unclear	No
Schoos (2013)[284]	Yes	Yes	Yes	Yes	Unclear	No
Schreiber (2012)[285]	Yes	Yes	Yes	No		
Sethi (2013)[286]	No					
Shand (2012)[287]	Yes	Yes	Unclear	Unclear	No	
Shortt (2013)[288]	No					
Spanuth (2011)[289]	Yes	Yes	Yes	Unclear	Unclear	No
Spasic-Obradovic (2011)[290]	Yes	Yes	Yes	Yes	No	
Stengaard (2012)[291]	Yes	Yes	Yes	Unclear	Unclear	No
Tajsic (2013)[292]	Yes	Yes	Yes	Unclear	Unclear	No
Tajsic (2013)[293]	Yes	Yes	Yes	Unclear	Unclear	No
Tajsic (2012)[294]	Yes	Yes	Yes	Unclear	No	
Tajsic (2013)[295]	Yes	Yes	Yes	Unclear	Unclear	No
Tamimi (2010)[296]	Yes	Yes	Yes	No		
Tanaka (2006)[297]	Yes	Yes	Yes	No		
Than (2012)[298]	Yes	Yes	Yes	No		
Thelin (2013)[299]	Yes	Yes	Yes	Yes	No	
Thomas (2007)[300]	Yes	No				
Thomas (2007)[301]	Yes	No				
Truong (2012)[302]	Yes	Yes	Yes	No		
Truong (2011)[303]	Yes	Yes	No	Unclear	Unclear	No
Twerenbold (2010)[304]	Yes	Yes	Yes	Yes	Unclear	No
Twerenbold (2010)[305]	Yes	Yes	Yes	Yes	Unclear	No
Twerenbold (2010)[306]	Yes	Yes	Yes	Yes	Unclear	No
Twerenbold (2011)[307]	Yes	Yes	Yes	No		
Twerenbold (2012)[308]	Yes	Yes	Yes	Yes	No	
University of Edinburgh (2013)[309]	Yes	Yes	Yes	Unclear	No	
University of Erlangen (2013)[310]	Yes	Yes	Yes	Unclear	Unclear	
Van Wijk (2012)[311]	Yes	Yes	Yes	Yes	No	
Vasikaran (2012)[312]	No					
Veljkovic (2012)[313]	Yes	Yes	Yes	Yes	Unclear	No
Venge (2008)[314]	Yes	No				
Venge (2009)[315]	Yes	No				
Venge (2010)[316]	Yes	No				

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome
Weber (2011)[317]	Yes	No				
Weber (2009)[318]	Yes	No				
Wildi (2012)[319]	Yes	Yes	Yes	No		
Wong (2010)[320]	Yes	No	Yes	No		
Worster (2013)[321]	Yes	No	Yes	Yes	No	No
Zahid (2009)[322]	Yes	Yes	Yes	Unclear	Unclear	No
Zahid (2008)[323]	Yes	Yes	Yes	No		
Zellweger (2012)[324]	Yes	Yes	Yes	Yes	No	
Zuily (2011)[325]	Yes	Yes	Yes	Yes	No	

Appendix 5 Sensitivity analyses (base case)

Deterministic base case

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2257	11.734	–£440	–0.015	£28,870				
Roche 99th centile	£2301	11.740	–£396	–0.010	£41,233	Abbott 99th centile	£44	0.006	£7777
Beckman 99th centile	£2327	11.743	–£370	–0.006	£58,988	Roche 99th centile	£26	0.003	£7777
Roche strategy	£2426	11.744	–£271	–0.006	£48,559	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2493	11.748	–£204	–0.002	£124,391	Beckman 99th centile	£167	0.005	£35,904
Standard Tn	£2697	11.749				Abbott strategy	£204	0.002	£124,391

Increased re-infarction and mortality risk for no treatment (vs. treated) = lifetime (instead of only during the first year after presentation at emergency department)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2257	11.677	–£440	–0.072	£6112				
Roche 99th centile	£2301	11.704	–£396	–0.045	£8731	Abbott 99th centile	£44	0.027	Extendedly dominated
Beckman 99th centile	£2327	11.720	–£370	–0.030	£12,493	Abbott 99th centile	£69	0.042	£1642
Roche strategy	£2426	11.723	–£271	–0.026	£10,284	Beckman 99th centile	£99	0.003	Extendedly dominated
Abbott strategy	£2493	11.741	–£204	–0.008	£26,352	Beckman 99th centile	£167	0.022	£7602
Standard Tn	£2697	11.749				Abbott strategy	£204	0.008	£26,352

No doctor on demand, but average waiting time before doctor becomes available is increased with 1, 2 or 3 hours

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Waiting time for doctor/decision pending delay = 1 hour(s)									
Abbott 99th centile	£2285	11.734	–£440	–0.015	£28,869				
Roche 99th centile	£2329	11.740	–£396	–0.010	£41,232	Abbott 99th centile	£44	0.006	Extendedly dominated
Beckman 99th centile	£2355	11.743	–£370	–0.006	£58,987	Abbott 99th centile	£70	0.009	£7776
Roche strategy	£2470	11.744	–£255	–0.006	£45,643	Beckman 99th centile	£115	0.001	Extendedly dominated
Abbott strategy	£2541	11.748	–£184	–0.002	£112,580	Beckman 99th centile	£186	0.005	£40,072
Standard Tn	£2725	11.749				Abbott strategy	£184	0.002	£112,580
Waiting time for doctor/decision pending delay = 2 hour(s)									
Abbott 99th centile	£2313	11.734	–£440	–0.015	£28,868				
Roche 99th centile	£2357	11.740	–£396	–0.010	£41,231	Abbott 99th centile	£44	0.006	Extendedly dominated
Beckman 99th centile	£2383	11.743	–£370	–0.006	£58,987	Abbott 99th centile	£70	0.009	£7776
Roche strategy	£2515	11.744	–£239	–0.006	£42,727	Beckman 99th centile	£132	0.001	Extendedly dominated
Abbott strategy	£2588	11.748	–£165	–0.002	£100,769	Beckman 99th centile	£205	0.005	£44,240
Standard Tn	£2754	11.749				Abbott strategy	£165	0.002	£100,769
Waiting time for doctor/decision pending delay = 3 hour(s)									
Abbott 99th centile	£2342	11.734	–£440	–0.015	£28,868				
Roche 99th centile	£2386	11.740	–£396	–0.010	£41,231	Abbott 99th centile	£44	0.006	Extendedly dominated
Beckman 99th centile	£2411	11.743	–£370	–0.006	£58,986	Abbott 99th centile	£70	0.009	£7775
Roche strategy	£2559	11.744	–£223	–0.006	£39,811	Beckman 99th centile	£148	0.001	Extendedly dominated
Abbott strategy	£2636	11.748	–£146	–0.002	£88,957	Beckman 99th centile	£225	0.005	£48,408
Standard Tn	£2782	11.749				Abbott strategy	£146	0.002	£88,957

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Doctor on demand at emergency department, but average waiting time before doctor becomes available in the general ward is increased with 1, 2 or 3 hours (discharge to general ward after 4 hours after presenting at emergency department)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Waiting time for doctor/decision pending delay = 1 hour(s)									
Abbott 99th centile	£2258	11.734	–£468	–0.015	£30,665				
Roche 99th centile	£2302	11.740	–£424	–0.010	£44,080	Abbott 99th centile	£44	0.006	£7776
Beckman 99th centile	£2327	11.743	–£398	–0.006	£63,347	Roche 99th centile	£26	0.003	£7776
Roche strategy	£2443	11.744	–£282	–0.006	£50,541	Beckman 99th centile	£115	0.001	Extendedly dominated
Abbott strategy	£2513	11.748	–£212	–0.002	£129,290	Beckman 99th centile	£186	0.005	£40,072
Standard Tn	£2725	11.749				Abbott strategy	£212	0.002	£129,290
Waiting time for doctor/decision pending delay = 2 hour(s)									
Abbott 99th centile	£2259	11.734	–£495	–0.015	£32,459				
Roche 99th centile	£2302	11.740	–£451	–0.010	£46,927	Abbott 99th centile	£44	0.006	£7776
Beckman 99th centile	£2328	11.743	–£425	–0.006	£67,705	Roche 99th centile	£26	0.003	£7776
Roche strategy	£2460	11.744	–£294	–0.006	£52,522	Beckman 99th centile	£132	0.001	Extendedly dominated
Abbott strategy	£2534	11.748	–£220	–0.002	£134,189	Beckman 99th centile	£205	0.005	£44,240
Standard Tn	£2754	11.749				Abbott strategy	£220	0.002	£134,189
Waiting time for doctor/decision pending delay = 3 hour(s)									
Abbott 99th centile	£2260	11.734	–£522	–0.015	£34,254				
Roche 99th centile	£2303	11.740	–£478	–0.010	£49,774	Abbott 99th centile	£44	0.006	£7775
Beckman 99th centile	£2329	11.743	–£453	–0.006	£72,064	Roche 99th centile	£26	0.003	£7775
Roche strategy	£2477	11.744	–£305	–0.006	£54,504	Beckman 99th centile	£148	0.001	Extendedly dominated
Abbott strategy	£2554	11.748	–£228	–0.002	£139,089	Beckman 99th centile	£225	0.005	£48,408
Standard Tn	£2782	11.749				Abbott strategy	£228	0.002	£139,089

Total delay of 1.5 hours

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2214	11.734	–£440	–0.015	£28,871				
Roche 99th centile	£2258	11.740	–£396	–0.010	£41,234	Abbott 99th centile	£44	0.006	£7778
Beckman 99th centile	£2284	11.743	–£370	–0.006	£58,989	Roche 99th centile	£26	0.003	£7778
Roche strategy	£2359	11.744	–£296	–0.006	£52,933	Beckman 99th centile	£75	0.001	Extendedly dominated
Abbott strategy	£2422	11.748	–£233	–0.002	£142,108	Beckman 99th centile	£138	0.005	£29,653
Standard Tn	£2655	11.749				Abbott strategy	£233	0.002	£142,108

Myocardial infarction treatment costs added for patients that were tested false-positive

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2456	11.734	–£241	–0.015	£15,824				
Abbott strategy	£2671	11.748	–£26	–0.002	£16,050	Abbott 99th centile	£215	0.014	£15,797
Standard Tn	£2697	11.749				Abbott strategy	£26	0.002	£16,050
Roche 99th centile	£2760	11.740	£63	–0.010	Dominated	Standard Tn	£63	–0.010	Dominated
Roche strategy	£2947	11.744	£251	–0.006	Dominated	Standard Tn	£251	–0.006	Dominated
Beckman 99th centile	£3038	11.743	£341	–0.006	Dominated	Standard Tn	£341	–0.006	Dominated

Myocardial infarction treatment costs added to first year of unstable angina

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2703	11.734	–£440	–0.015	£28,870				
Roche 99th centile	£2747	11.740	–£396	–0.010	£41,233	Abbott 99th centile	£44	0.006	£7777
Beckman 99th centile	£2773	11.743	–£370	–0.006	£58,988	Roche 99th centile	£26	0.003	£7777
Roche strategy	£2872	11.744	–£271	–0.006	£48,559	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2940	11.748	–£204	–0.002	£124,391	Beckman 99th centile	£167	0.005	£35,904
Standard Tn	£3144	11.749				Abbott strategy	£204	0.002	£124,391

Test costs

Strategy	Costs	QALYs	Compared with standard Tn			Compared with next best strategy			
			ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Test costs = £5									
Abbott 99th centile	£2240	11.734	–£425	–0.015	£27,856				
Roche 99th centile	£2284	11.740	–£381	–0.010	£39,624	Abbott 99th centile	£44	0.006	£7778
Beckman 99th centile	£2310	11.743	–£355	–0.006	£56,526	Roche 99th centile	£26	0.003	£7778
Roche strategy	£2400	11.744	–£265	–0.006	£47,439	Beckman 99th centile	£90	0.001	Extendedly dominated
Abbott strategy	£2466	11.748	–£199	–0.002	£121,624	Beckman 99th centile	£156	0.005	£33,550
Standard Tn	£2665	11.749				Abbott strategy	£199	0.002	£121,624
Test costs = £40									
Abbott 99th centile	£2278	11.734	–£460	–0.015	£30,150				
Roche 99th centile	£2322	11.740	–£416	–0.010	£43,264	Abbott 99th centile	£44	0.006	Extendedly dominated
Beckman 99th centile	£2348	11.743	–£390	–0.006	£62,097	Abbott 99th centile	£70	0.009	£7776
Roche strategy	£2458	11.744	–£279	–0.006	£49,972	Beckman 99th centile	£111	0.001	Extendedly dominated
Abbott strategy	£2528	11.748	–£210	–0.002	£127,886	Beckman 99th centile	£180	0.005	£38,878
Standard Tn	£2737	11.749				Abbott strategy	£210	0.002	£127,886

Acute myocardial infarction treatment costs

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
AMI treatment costs = £2577									
Abbott 99th centile	£2119	11.734	–£415	–0.015	£27,188				
Roche 99th centile	£2154	11.740	–£380	–0.010	£39,551	Abbott 99th centile	£34	0.006	Extendedly dominated
Beckman 99th centile	£2174	11.743	–£360	–0.006	£57,307	Abbott 99th centile	£55	0.009	£6096
Roche strategy	£2272	11.744	–£262	–0.006	£46,877	Beckman 99th centile	£98	0.001	Extendedly dominated
Abbott strategy	£2333	11.748	–£201	–0.002	£122,710	Beckman 99th centile	£159	0.005	£34,223
Standard Tn	£2534	11.749				Roche strategy	£201	0.002	£122,710
AMI treatment costs = £4295									
Abbott 99th centile	£2394	11.734	–£466	–0.015	£30,551	Abbott 99th centile	£53	0.006	£9458
Roche 99th centile	£2448	11.740	–£413	–0.010	£42,914	Roche 99th centile	£32	0.003	£9458
Beckman 99th centile	£2479	11.743	–£381	–0.006	£60,669	Beckman 99th centile	£100	0.001	Extendedly dominated
Roche strategy	£2579	11.744	–£281	–0.006	£50,240	Beckman 99th centile	£174	0.005	£37,586
Abbott strategy	£2654	11.748	–£207	–0.002	£126,073	Roche strategy	£207	0.002	£126,073
Standard Tn	£2860	11.749							

Post-myocardial infarction health-state costs

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Post-MI health-state costs (first year) = £6791									
Abbott 99th centile	£2393	11.734	–£443	–0.015	£29,024				
Roche 99th centile	£2438	11.740	–£398	–0.010	£41,387	Abbott 99th centile	£45	0.006	£7931
Beckman 99th centile	£2464	11.743	–£371	–0.006	£59,142	Roche 99th centile	£26	0.003	£7931
Roche strategy	£2563	11.744	–£272	–0.006	£48,713	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2632	11.748	–£204	–0.002	£124,545	Beckman 99th centile	£167	0.005	£36,059
Standard Tn	£2836	11.749				Abbott strategy	£204	0.002	£124,545
Post-MI health-state costs (first year) = £4879									
Abbott 99th centile	£2121	11.734	–£438	–0.015	£28,715				
Roche 99th centile	£2164	11.740	–£395	–0.010	£41,078	Abbott 99th centile	£43	0.006	£7623
Beckman 99th centile	£2189	11.743	–£369	–0.006	£58,834	Roche 99th centile	£25	0.003	£7623
Roche strategy	£2288	11.744	–£271	–0.006	£48,405	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2355	11.748	–£204	–0.002	£124,237	Beckman 99th centile	£166	0.005	£35,750
Standard Tn	£2558	11.749				Abbott strategy	£204	0.002	£124,237

Utility difference between unstable angina and acute myocardial infarction

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Utility difference between UA and AMI = 0.12									
Abbott 99th centile	£2257	11.779	–£440	–0.015	£28,870				
Roche 99th centile	£2301	11.785	–£396	–0.010	£41,233	Abbott 99th centile	£44	0.006	£7777
Beckman 99th centile	£2327	11.788	–£370	–0.006	£58,988	Roche 99th centile	£26	0.003	£7777
Roche strategy	£2426	11.789	–£271	–0.006	£48,559	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2493	11.793	–£204	–0.002	£124,391	Beckman 99th centile	£167	0.005	£35,904
Standard Tn	£2697	11.794				Abbott strategy	£204	0.002	£124,391
Utility difference between UA and AMI = –0.10									
Abbott 99th centile	£2257	11.581	–£440	–0.015	£28,870				
Roche 99th centile	£2301	11.587	–£396	–0.010	£41,233	Abbott 99th centile	£44	0.006	Extendedly dominated
Beckman 99th centile	£2327	11.590	–£370	–0.006	£58,988	Abbott 99th centile	£70	0.009	£7777
Roche strategy	£2426	11.591	–£271	–0.006	£48,559	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2493	11.595	–£204	–0.002	£124,391	Beckman 99th centile	£167	0.005	£35,904
Standard Tn	£2697	11.597				Abbott strategy	£204	0.002	£124,391

Myocardial infarction disutility

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
MI disutility = –0.059 (age = 45 years); –0.050 (age = 55 years); –0.024 (age = 65 years); –0.006 (age = 75+ years)									
Abbott 99th centile	£2257	11.735	–£440	–0.015	£28,832				
Roche 99th centile	£2301	11.741	–£396	–0.010	£41,178	Abbott 99th centile	£44	0.006	£7767
Beckman 99th centile	£2327	11.744	–£370	–0.006	£58,910	Roche 99th centile	£26	0.003	£7767
Roche strategy	£2426	11.745	–£271	–0.006	£48,495	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2493	11.749	–£204	–0.002	£124,227	Beckman 99th centile	£167	0.005	£35,857
Standard Tn	£2697	11.751				Abbott strategy	£204	0.002	£124,227
MI disutility = –0.061 (age = 45 years); –0.052 (age = 55 years); –0.026 (age = 65 years); –0.008 (age = 75+ years)									
Abbott 99th centile	£2257	11.733	–£440	–0.015	£28,908				
Roche 99th centile	£2301	11.738	–£396	–0.010	£41,287	Abbott 99th centile	£44	0.006	Extendedly dominated
Beckman 99th centile	£2327	11.742	–£370	–0.006	£59,066	Abbott 99th centile	£70	0.009	£7787
Roche strategy	£2426	11.742	–£271	–0.006	£48,623	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2493	11.746	–£204	–0.002	£124,556	Beckman 99th centile	£167	0.005	£35,952
Standard Tn	£2697	11.748				Abbott strategy	£204	0.002	£124,556

Mortality (30-day) treated acute myocardial infarction (decision tree)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Mortality (30-day) treated AMI = 0.120									
Abbott 99th centile	£2219	11.710	–£432	–0.010	£41,819				
Roche 99th centile	£2260	11.714	–£391	–0.007	£60,062	Abbott 99th centile	£41	0.004	£10,692
Beckman 99th centile	£2284	11.716	–£367	–0.004	£86,264	Roche 99th centile	£24	0.002	£10,692
Roche strategy	£2383	11.717	–£268	–0.004	£70,874	Beckman 99th centile	£99	0.000	Extendedly dominated
Abbott strategy	£2448	11.719	–£203	–0.001	£182,781	Beckman 99th centile	£164	0.003	£52,200
Standard Tn	£2651	11.721				Abbott strategy	£203	0.001	£182,781
Mortality (30-day) treated AMI = 0.074									
Abbott 99th centile	£2295	11.758	–£448	–0.020	£22,206				
Roche 99th centile	£2342	11.765	–£401	–0.013	£31,543	Abbott 99th centile	£47	0.007	Extendedly dominated
Beckman 99th centile	£2369	11.770	–£374	–0.008	£44,952	Abbott 99th centile	£75	0.012	£6277
Roche strategy	£2469	11.771	–£274	–0.007	£37,076	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2538	11.776	–£205	–0.002	£94,345	Beckman 99th centile	£169	0.006	£27,519
Standard Tn	£2743	11.778				Abbott strategy	£205	0.002	£94,345

Mortality (30-day) untreated acute myocardial infarction (decision tree)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Mortality (30-day) untreated AMI = 0.240									
Abbott 99th centile	£2227	11.707	–£470	–0.042	£11,153				
Roche 99th centile	£2282	11.723	–£415	–0.027	£15,623	Abbott 99th centile	£55	0.016	Extendedly dominated
Beckman 99th centile	£2314	11.732	–£383	–0.017	£22,042	Abbott 99th centile	£88	0.025	£3528
Roche strategy	£2414	11.734	–£282	–0.015	£18,271	Beckman 99th centile	£100	0.002	Extendedly dominated
Abbott strategy	£2490	11.745	–£207	–0.005	£45,686	Beckman 99th centile	£176	0.013	£13,697
Standard Tn	£2697	11.749				Abbott strategy	£207	0.005	£45,686
Mortality (30-day) untreated AMI = 0.000									
Abbott 99th centile	£2280	11.755	–£417	0.006	Dominant				
Roche 99th centile	£2316	11.753	–£381	0.004	Dominant	Abbott 99th centile	£35	–0.002	Dominated
Beckman 99th centile	£2336	11.752	–£361	0.002	Dominant	Abbott 99th centile	£56	–0.003	Dominated
Roche strategy	£2434	11.751	–£263	0.002	Dominant	Abbott 99th centile	£154	–0.004	Dominated
Abbott strategy	£2496	11.750	–£201	0.001	Dominant	Abbott 99th centile	£215	–0.005	Dominated
Standard Tn	£2697	11.749				Abbott 99th centile	£417	–0.006	Dominated

Annual re-infarction probability (after initial acute myocardial infarction)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Annual re-infarction (after initial AMI) = 0.26									
Abbott 99th centile	£2286	11.722	–£440	–0.015	£28,543				
Roche 99th centile	£2330	11.728	–£397	–0.010	£40,757	Abbott 99th centile	£44	0.006	£7704
Beckman 99th centile	£2356	11.731	–£371	–0.006	£58,299	Roche 99th centile	£26	0.003	£7704
Roche strategy	£2455	11.732	–£272	–0.006	£47,995	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2523	11.736	–£204	–0.002	£122,916	Beckman 99th centile	£167	0.005	£35,493
Standard Tn	£2727	11.737				Abbott strategy	£204	0.002	£122,916
Annual re-infarction (after initial AMI) = 0.19									
Abbott 99th centile	£2227	11.746	–£440	–0.015	£29,218				
Roche 99th centile	£2270	11.752	–£396	–0.009	£41,738	Abbott 99th centile	£44	0.006	Extendedly dominated
Beckman 99th centile	£2296	11.755	–£370	–0.006	£59,719	Abbott 99th centile	£70	0.009	£7856
Roche strategy	£2395	11.756	–£271	–0.006	£49,157	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2463	11.760	–£204	–0.002	£125,955	Beckman 99th centile	£167	0.005	£36,342
Standard Tn	£2666	11.761				Abbott strategy	£204	0.002	£125,955

Relativer risk re-infarction (untreated compared with treated)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
RR re-infarction (untreated vs. treated) = 5.15									
Abbott 99th centile	£2259	11.730	–£438	–0.019	£22,555				
Roche 99th centile	£2302	11.737	–£395	–0.012	£32,258	Abbott 99th centile	£43	0.007	£5999
Beckman 99th centile	£2327	11.741	–£370	–0.008	£46,195	Roche 99th centile	£25	0.004	£5999
Roche strategy	£2426	11.742	–£271	–0.007	£38,009	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2493	11.747	–£204	–0.002	£97,530	Beckman 99th centile	£166	0.006	£28,076
Standard Tn	£2697	11.749				Abbott strategy	£204	0.002	£97,530
RR re-infarction (untreated vs. treated) = 1.28									
	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2256	11.736	–£441	–0.013	£33,518				
Roche 99th centile	£2300	11.741	–£397	–0.008	£47,838	Abbott 99th centile	£44	0.005	Extendedly dominated
Beckman 99th centile	£2326	11.744	–£371	–0.005	£68,404	Abbott 99th centile	£70	0.008	£9086
Roche strategy	£2425	11.744	–£272	–0.005	£56,324	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2493	11.748	–£204	–0.001	£144,162	Beckman 99th centile	£167	0.004	£41,666
Standard Tn	£2697	11.749				Abbott strategy	£204	0.001	£144,162

Annual post-myocardial infarction mortality

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Annual post-MI mortality = 0.068									
Abbott 99th centile	£2248	11.715	–£440	–0.015	£28,843				
Roche 99th centile	£2292	11.721	–£396	–0.010	£41,191	Abbott 99th centile	£44	0.006	£7777
Beckman 99th centile	£2318	11.724	–£370	–0.006	£58,924	Roche 99th centile	£26	0.003	£7777
Roche strategy	£2417	11.725	–£271	–0.006	£48,508	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2485	11.729	–£204	–0.002	£124,247	Beckman 99th centile	£167	0.005	£35,869
Standard Tn	£2688	11.731				Abbott strategy	£204	0.002	£124,247
Annual post-MI mortality = 0.065									
Abbott 99th centile	£2266	11.753	–£440	–0.015	£28,897				
Roche 99th centile	£2309	11.758	–£396	–0.010	£41,275	Abbott 99th centile	£44	0.006	£7777
Beckman 99th centile	£2335	11.762	–£370	–0.006	£59,053	Roche 99th centile	£26	0.003	£7777
Roche strategy	£2434	11.762	–£271	–0.006	£48,610	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2502	11.766	–£204	–0.002	£124,538	Beckman 99th centile	£167	0.005	£35,940
Standard Tn	£2706	11.768				Abbott strategy	£204	0.002	£124,538

Annual mortality post myocardial infarction after re-infarction

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Annual mortality post-MI with re-infarction = 0.137									
Abbott 99th centile	£2258	11.737	–£440	–0.015	£28,946				
Roche 99th centile	£2302	11.742	–£396	–0.010	£41,341	Abbott 99th centile	£44	0.006	£7797
Beckman 99th centile	£2328	11.746	–£370	–0.006	£59,144	Roche 99th centile	£26	0.003	£7797
Roche strategy	£2427	11.746	–£271	–0.006	£48,687	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2494	11.750	–£204	–0.002	£124,721	Beckman 99th centile	£167	0.005	£35,999
Standard Tn	£2698	11.752				Abbott strategy	£204	0.002	£124,721
Annual mortality post-MI with re-infarction = 0.146									
Abbott 99th centile	£2256	11.731	–£440	–0.015	£28,795				
Roche 99th centile	£2300	11.737	–£396	–0.010	£41,126	Abbott 99th centile	£44	0.006	£7758
Beckman 99th centile	£2325	11.740	–£370	–0.006	£58,835	Roche 99th centile	£26	0.003	£7758
Roche strategy	£2424	11.741	–£271	–0.006	£48,433	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2492	11.745	–£204	–0.002	£124,067	Beckman 99th centile	£167	0.005	£35,812
Standard Tn	£2696	11.746				Abbott strategy	£204	0.002	£124,067

Hazard ratio mortality (unstable angina compared with non-ST segment elevation myocardial infarction)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
HR mortality (UA vs. NSTEMI) = 1.053									
Abbott 99th centile	£2205	11.558	–£440	–0.015	£28,870				
Roche 99th centile	£2249	11.564	–£396	–0.010	£41,233	Abbott 99th centile	£44	0.006	Extendedly dominated
Beckman 99th centile	£2274	11.567	–£370	–0.006	£58,988	Abbott 99th centile	£70	0.009	£7777
Roche strategy	£2374	11.568	–£271	–0.006	£48,559	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2441	11.572	–£204	–0.002	£124,391	Beckman 99th centile	£167	0.005	£35,904
Standard Tn	£2645	11.573				Abbott strategy	£204	0.002	£124,391
HR mortality (UA vs. NSTEMI) = 0.581									
Abbott 99th centile	£2306	11.898	–£440	–0.015	£28,870				
Roche 99th centile	£2349	11.904	–£396	–0.010	£41,233	Abbott 99th centile	£44	0.006	£7777
Beckman 99th centile	£2375	11.907	–£370	–0.006	£58,988	Roche 99th centile	£26	0.003	£7777
Roche strategy	£2474	11.908	–£271	–0.006	£48,559	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2542	11.912	–£204	–0.002	£124,391	Beckman 99th centile	£167	0.005	£35,904
Standard Tn	£2746	11.913				Abbott strategy	£204	0.002	£124,391

Relative risk mortality (untreated vs. treated acute myocardial infarction)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
RR mortality (untreated vs. treated AMI) = 3.908									
Abbott 99th centile	£2224	11.709	–£472	–0.040	£11,771				
Roche 99th centile	£2280	11.724	–£417	–0.025	£16,467	Abbott 99th centile	£56	0.015	£3759
Beckman 99th centile	£2313	11.733	–£384	–0.017	£23,212	Roche 99th centile	£33	0.009	£3759
Roche strategy	£2414	11.734	–£283	–0.015	£19,250	Beckman 99th centile	£100	0.002	Extendedly dominated
Abbott strategy	£2490	11.745	–£207	–0.004	£48,054	Beckman 99th centile	£176	0.012	£14,443
Standard Tn	£2697	11.749				Abbott strategy	£207	0.004	£48,054
RR mortality (untreated vs. treated AMI) = 0.901									
Abbott 99th centile	£2272	11.746	–£425	–0.003	£128,875				
Roche 99th centile	£2310	11.747	–£387	–0.002	£186,080	Abbott 99th centile	£38	0.001	Extendedly dominated
Beckman 99th centile	£2333	11.748	–£364	–0.001	£268,237	Abbott 99th centile	£61	0.002	£31,275
Roche strategy	£2431	11.748	–£266	–0.001	£219,979	Beckman 99th centile	£98	0.000	Extendedly dominated
Abbott strategy	£2495	11.749	–£202	0.000	£570,869	Beckman 99th centile	£162	0.001	£161,425
Standard Tn	£2697	11.749				Abbott strategy	£202	0.000	£570,869

Appendix 6 Sensitivity analyses (secondary analysis)

Deterministic secondary analysis

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2789	11.530	–£276	0.036	Dominant				
Roche 99th centile	£2832	11.532	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2858	11.532	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2957	11.535	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3025	11.543	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,047
Standard Tn	£3064	11.493				Abbott strategy	£39	–0.050	Dominated

Increased re-infarction and mortality risk for no treatment (vs. treated) = lifetime (instead of only during the first year after presentation at emergency)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2789	11.473	–£286	0.089	Dominant				
Roche 99th centile	£2833	11.496	–£242	0.113	Dominant	Abbott 99th centile	£43	0.023	£1853
Beckman 99th centile	£2858	11.509	–£217	0.126	Dominant	Roche 99th centile	£26	0.013	£2017
Roche strategy	£2957	11.515	–£118	0.131	Dominant	Beckman 99th centile	£99	0.006	Extendedly dominated
Abbott strategy	£3025	11.537	–£50	0.154	Dominant	Beckman 99th centile	£167	0.028	£5889
Standard Tn	£3075	11.383				Abbott strategy	£50	–0.154	Dominated

No doctor on demand, but average waiting time before doctor becomes available is increased with 1, 2 or 3 hours

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Waiting time for doctor/decision pending delay = 1 hour(s)									
Abbott 99th centile	£2817	11.530	–£275	0.036	Dominant				
Roche 99th centile	£2861	11.532	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	£17,587
Beckman 99th centile	£2887	11.532	–£206	0.039	Dominant	Roche 99th centile	£26	0.000	Extendedly dominated
Roche strategy	£3002	11.535	–£91	0.042	Dominant	Roche 99th centile	£141	0.003	Extendedly dominated
Abbott strategy	£3073	11.543	–£20	0.050	Dominant	Roche 99th centile	£212	0.011	£18,628
Standard Tn	£3093	11.493				Abbott strategy	£20	–0.050	Dominated
Waiting time for doctor/decision pending delay = 2 hour(s)									
Abbott 99th centile	£2846	11.530	–£275	0.036	Dominant				
Roche 99th centile	£2890	11.532	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	£17,586
Beckman 99th centile	£2915	11.532	–£206	0.039	Dominant	Roche 99th centile	£26	0.000	Extendedly dominated
Roche strategy	£3047	11.535	–£74	0.042	Dominant	Roche 99th centile	£157	0.003	Extendedly dominated
Abbott strategy	£3121	11.543	£0	0.050	Dominant	Roche 99th centile	£232	0.011	£20,326
Standard Tn	£3121	11.493				Abbott strategy	£0	–0.050	Dominated
Waiting time for doctor/decision pending delay = 3 hour(s)									
Abbott 99th centile	£2875	11.530	–£275	0.036	Dominant				
Roche 99th centile	£2918	11.532	–£231	0.039	Dominant	Abbott 99th centile	£44	0.002	£17,584
Beckman 99th centile	£2944	11.532	–£206	0.039	Dominant	Roche 99th centile	£26	0.000	Extendedly dominated
Roche strategy	£3092	11.535	–£58	0.042	Dominant	Roche 99th centile	£174	0.003	Extendedly dominated
Standard Tn	£3149	11.493				Roche 99th centile	£231	–0.039	Dominated
Abbott strategy	£3169	11.543	£20	0.050	£390	Roche 99th centile	£251	0.011	£22,024

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Doctor on demand at emergency department, but average waiting time before doctor becomes available in the general ward is increased with 1, 2 or 3 hours (discharge to general ward after 4 hours after presenting at emergency department)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Waiting time for doctor/decision pending delay = 1 hour(s)									
Abbott 99th centile	£2790	11.530	–£303	0.036	Dominant				
Roche 99th centile	£2834	11.532	–£259	0.039	Dominant	Abbott 99th centile	£44	0.002	£17,587
Beckman 99th centile	£2859	11.532	–£234	0.039	Dominant	Roche 99th centile	£26	0.000	Extendedly dominated
Roche strategy	£2975	11.535	–£118	0.042	Dominant	Roche 99th centile	£141	0.003	Extendedly dominated
Abbott strategy	£3046	11.543	–£47	0.050	Dominant	Roche 99th centile	£212	0.011	£18,628
Standard Tn	£3093	11.493				Abbott strategy	£47	–0.050	Dominated
Waiting time for doctor/decision pending delay = 2 hour(s)									
Abbott 99th centile	£2791	11.530	–£330	0.036	Dominant				
Roche 99th centile	£2835	11.532	–£286	0.039	Dominant	Abbott 99th centile	£44	0.002	£17,586
Beckman 99th centile	£2860	11.532	–£261	0.039	Dominant	Roche 99th centile	£26	0.000	Extendedly dominated
Roche strategy	£2992	11.535	–£129	0.042	Dominant	Roche 99th centile	£157	0.003	Extendedly dominated
Abbott strategy	£3066	11.543	–£55	0.050	Dominant	Roche 99th centile	£232	0.011	£20,326
Standard Tn	£3121	11.493				Abbott strategy	£55	–0.050	Dominated
Waiting time for doctor/decision pending delay = 3 hour(s)									
Abbott 99th centile	£2792	11.530	–£357	0.036	Dominant				
Roche 99th centile	£2836	11.532	–£313	0.039	Dominant	Abbott 99th centile	£44	0.002	£17,584
Beckman 99th centile	£2862	11.532	–£288	0.039	Dominant	Roche 99th centile	£26	0.000	Extendedly dominated
Roche strategy	£3010	11.535	–£140	0.042	Dominant	Roche 99th centile	£174	0.003	Extendedly dominated
Abbott strategy	£3087	11.543	–£63	0.050	Dominant	Roche 99th centile	£251	0.011	£22,024
Standard Tn	£3149	11.493				Abbott strategy	£63	–0.050	Dominated

Total delay of 1.5 hours

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2746	11.530	–£276	0.036	Dominant				
Roche 99th centile	£2790	11.532	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2815	11.532	–£207	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2890	11.535	–£132	0.042	Dominant	Abbott 99th centile	£144	0.006	Extendedly dominated
Abbott strategy	£2953	11.543	–£69	0.050	Dominant	Abbott 99th centile	£207	0.014	£14,956
Standard Tn	£3022	11.493				Abbott strategy	£69	–0.050	Dominated

Myocardial infarction treatment costs added for patients that were tested false-positive

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2841	11.530	–£224	0.036	Dominant				
Abbott strategy	£3056	11.543	–£9	0.050	Dominant	Abbott 99th centile	£215	0.014	£15,507
Standard Tn	£3064	11.493	£0	0.000		Abbott strategy	£9	–0.050	Dominated
Roche 99th centile	£3144	11.532	£80	0.039	£2065	Abbott strategy	£89	–0.011	Dominated
Roche strategy	£3331	11.535	£267	0.042	£6360	Abbott strategy	£275	–0.008	Dominated
Beckman 99th centile	£3421	11.532	£356	0.039	£9142	Abbott strategy	£365	–0.011	Dominated

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Myocardial infarction treatment costs added to first year of unstable angina

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£3212	11.530	–£275	0.036	Dominant				
Roche 99th centile	£3256	11.532	–£231	0.039	Dominant	Abbott 99th centile	£43	0.002	Extendedly dominated
Beckman 99th centile	£3281	11.532	–£205	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£3381	11.535	–£106	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3449	11.543	–£38	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,048
Standard Tn	£3487	11.493				Abbott strategy	£38	–0.050	Dominated

Test costs

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Test costs = £5									
Abbott 99th centile	£2772	11.530	–£260	0.036	Dominant				
Roche 99th centile	£2816	11.532	–£217	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2841	11.532	–£191	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2931	11.535	–£101	0.042	Dominant	Abbott 99th centile	£159	0.006	Extendedly dominated
Abbott strategy	£2997	11.543	–£35	0.050	Dominant	Abbott 99th centile	£225	0.014	£16,260
Standard Tn	£3032	11.493				Abbott strategy	£35	–0.050	Dominated
Test costs = £40									
Abbott 99th centile	£2810	11.530	–£295	0.036	Dominant				
Roche 99th centile	£2854	11.532	–£252	0.039	Dominant	Abbott 99th centile	£44	0.002	£17,586
Beckman 99th centile	£2879	11.532	–£226	0.039	Dominant	Roche 99th centile	£26	0.000	Extendedly dominated
Roche strategy	£2990	11.535	–£115	0.042	Dominant	Roche 99th centile	£137	0.003	Extendedly dominated
Abbott strategy	£3060	11.543	–£45	0.050	Dominant	Roche 99th centile	£207	0.011	£18,141
Standard Tn	£3105	11.493				Abbott strategy	£45	–0.050	Dominated

Acute myocardial infarction

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
AMI treatment costs = £2577									
Abbott 99th centile	£2607	11.530	–£286	0.036	Dominant				
Roche 99th centile	£2641	11.532	–£252	0.039	Dominant	Abbott 99th centile	£34	0.002	£13,770
Beckman 99th centile	£2661	11.532	–£232	0.039	Dominant	Roche 99th centile	£20	0.000	Extendedly dominated
Roche strategy	£2759	11.535	–£134	0.042	Dominant	Roche 99th centile	£118	0.003	Extendedly dominated
Abbott strategy	£2820	11.543	–£73	0.050	Dominant	Roche 99th centile	£179	0.011	£15,751
Standard Tn	£2893	11.493				Abbott strategy	£73	–0.050	Dominated
AMI treatment costs = £4295									
Abbott 99th centile	£2971	11.530	–£265	0.036	Dominant				
Roche 99th centile	£3024	11.532	–£212	0.039	Dominant	Abbott 99th centile	£53	0.002	Extendedly dominated
Beckman 99th centile	£3055	11.532	–£181	0.039	Dominant	Abbott 99th centile	£84	0.003	Extendedly dominated
Roche strategy	£3155	11.535	–£81	0.042	Dominant	Abbott 99th centile	£185	0.006	Extendedly dominated
Abbott strategy	£3230	11.543	–£6	0.050	Dominant	Abbott 99th centile	£259	0.014	£18,698
Standard Tn	£3236	11.493				Abbott strategy	£6	–0.050	Dominated

Post-myocardial infarction health-state costs

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Post MI health-state costs (first year) = £6791									
Abbott 99th centile	£2970	11.530	–£276	0.036	Dominant				
Roche 99th centile	£3014	11.532	–£231	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£3040	11.532	–£205	0.039	Dominant	Abbott 99th centile	£71	0.003	Extendedly dominated
Roche strategy	£3139	11.535	–£106	0.042	Dominant	Abbott 99th centile	£170	0.006	Extendedly dominated
Abbott strategy	£3208	11.543	–£37	0.050	Dominant	Abbott 99th centile	£239	0.014	£17,199
Standard Tn	£3245	11.493				Abbott strategy	£37	–0.050	Dominated
Post MI health-state costs (first year) = £4879									
Abbott 99th centile	£2608	11.530	–£275	0.036	Dominant				
Roche 99th centile	£2651	11.532	–£233	0.039	Dominant	Abbott 99th centile	£43	0.002	Extendedly dominated
Beckman 99th centile	£2676	11.532	–£207	0.039	Dominant	Abbott 99th centile	£68	0.003	Extendedly dominated
Roche strategy	£2775	11.535	–£108	0.042	Dominant	Abbott 99th centile	£167	0.006	Extendedly dominated
Abbott strategy	£2842	11.543	–£41	0.050	Dominant	Abbott 99th centile	£234	0.014	£16,896
Standard Tn	£2883	11.493				Abbott strategy	£41	–0.050	Dominated

Utility difference between unstable angina and acute myocardial infarction

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Utility difference between UA and AMI = 0.12									
Abbott 99th centile	£2789	11.572	–£276	0.036	Dominant				
Roche 99th centile	£2832	11.575	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2858	11.575	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2957	11.578	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3025	11.586	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,046
Standard Tn	£3064	11.536				Abbott strategy	£39	–0.050	Dominated
Utility difference between UA and AMI = –0.10									
Abbott 99th centile	£2789	11.385	–£276	0.036	Dominant				
Roche 99th centile	£2832	11.387	–£232	0.038	Dominant	Abbott 99th centile	£44	0.003	Extendedly dominated
Beckman 99th centile	£2858	11.388	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2957	11.391	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3025	11.399	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,051
Standard Tn	£3064	11.349				Abbott strategy	£39	–0.050	Dominated

Myocardial infarction disutility

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
MI disutility = –0.059 (age = 45 years); –0.050 (age = 55 years); –0.024 (age = 65 years); –0.006 (age = 75 + years)									
Abbott 99th centile	£2789	11.531	–£276	0.036	Dominant				
Roche 99th centile	£2832	11.534	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2858	11.534	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2957	11.537	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3025	11.545	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,025
Standard Tn	£3064	11.495				Abbott strategy	£39	–0.050	Dominated
MI disutility = –0.061 (age = 45 years); –0.052 (age = 55 years); –0.026 (age = 65 years); –0.008 (age = 75 + years)									
Abbott 99th centile	£2789	11.528	–£276	0.036	Dominant				
Roche 99th centile	£2832	11.530	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2858	11.531	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2957	11.534	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3025	11.542	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,070
Standard Tn	£3064	11.492				Abbott strategy	£39	–0.050	Dominated

Mortality (30-day) treated acute myocardial infarction (decision tree)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Mortality (30-day) treated AMI = 0.120									
Abbott 99th centile	£2750	11.504	–£269	0.039	Dominant				
Roche 99th centile	£2790	11.504	–£228	0.039	Dominant	Abbott 99th centile	£41	0.000	Dominated
Beckman 99th centile	£2814	11.502	–£205	0.038	Dominant	Abbott 99th centile	£64	–0.002	Dominated
Roche strategy	£2913	11.506	–£106	0.041	Dominant	Abbott 99th centile	£163	0.002	Extendedly dominated
Abbott strategy	£2979	11.514	–£40	0.049	Dominant	Abbott 99th centile	£229	0.010	£24,010
Standard Tn	£3019	11.465				Abbott strategy	£40	–0.049	Dominated
Mortality (30-day) treated AMI = 0.074									
Abbott 99th centile	£2828	11.555	–£282	0.033	Dominant				
Roche 99th centile	£2875	11.560	–£236	0.038	Dominant	Abbott 99th centile	£47	0.005	£9175
Beckman 99th centile	£2902	11.562	–£208	0.040	Dominant	Roche 99th centile	£28	0.002	£12,967
Roche strategy	£3002	11.565	–£109	0.043	Dominant	Beckman 99th centile	£100	0.003	Extendedly dominated
Abbott strategy	£3072	11.574	–£39	0.051	Dominant	Beckman 99th centile	£170	0.011	£15,399
Standard Tn	£3111	11.522				Abbott strategy	£39	–0.051	Dominated

Mortality (30-day) untreated acute myocardial infarction (decision tree)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Mortality (30-day) untreated AMI = 0.240									
Abbott 99th centile	£2759	11.503	–£294	0.066	Dominant				
Roche 99th centile	£2813	11.515	–£239	0.079	Dominant	Abbott 99th centile	£55	0.012	£4404
Beckman 99th centile	£2846	11.521	–£207	0.085	Dominant	Roche 99th centile	£32	0.006	£5228
Roche strategy	£2946	11.525	–£106	0.089	Dominant	Beckman 99th centile	£101	0.004	Extendedly dominated
Abbott strategy	£3022	11.541	–£30	0.104	Dominant	Beckman 99th centile	£176	0.019	£9139
Standard Tn	£3052	11.436				Abbott strategy	£30	–0.104	Dominated
Mortality (30-day) untreated AMI = 0.000									
Abbott 99th centile	£2813	11.551	–£262	0.013	Dominant				
Roche 99th centile	£2847	11.545	–£227	0.007	Dominant	Abbott 99th centile	£35	–0.005	Dominated
Beckman 99th centile	£2868	11.541	–£206	0.003	Dominant	Abbott 99th centile	£55	–0.010	Dominated
Roche strategy	£2966	11.543	–£108	0.005	Dominant	Abbott 99th centile	£153	–0.008	Dominated
Abbott strategy	£3028	11.546	–£46	0.008	Dominant	Abbott 99th centile	£215	–0.005	Dominated
Standard Tn	£3074	11.538				Abbott 99th centile	£262	–0.013	Dominated

Annual re-infarction probability (after initial acute myocardial infarction)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Annual re-infarction (after initial AMI) = 0.26									
Abbott 99th centile	£2830	11.515	–£275	0.036	Dominant				
Roche 99th centile	£2873	11.517	–£232	0.039	Dominant	Abbott 99th centile	£44	0.003	Extendedly dominated
Beckman 99th centile	£2899	11.517	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2998	11.520	–£107	0.042	Dominant	Abbott 99th centile	£169	0.006	Extendedly dominated
Abbott strategy	£3066	11.529	–£39	0.050	Dominant	Abbott 99th centile	£237	0.014	£16,867
Standard Tn	£3105	11.478				Abbott strategy	£39	–0.050	Dominated
Annual re-infarction (after initial AMI) = 0.19									
Abbott 99th centile	£2747	11.545	–£276	0.036	Dominant				
Roche 99th centile	£2791	11.547	–£233	0.038	Dominant	Abbott 99th centile	£43	0.002	Extendedly dominated
Beckman 99th centile	£2817	11.548	–£207	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2916	11.551	–£108	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£2984	11.559	–£40	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,241
Standard Tn	£3023	11.509				Abbott strategy	£40	–0.050	Dominated

Relative risk re-infarction (untreated vs. treated)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
RR re-infarction (untreated vs. treated) = 5.15									
Abbott 99th centile	£2791	11.525	–£277	0.036	Dominant				
Roche 99th centile	£2834	11.529	–£234	0.041	Dominant	Abbott 99th centile	£43	0.004	£10,647
Beckman 99th centile	£2859	11.531	–£209	0.042	Dominant	Roche 99th centile	£25	0.001	Extendedly dominated
Roche strategy	£2958	11.534	–£110	0.045	Dominant	Roche 99th centile	£124	0.004	Extendedly dominated
Abbott strategy	£3025	11.543	–£43	0.054	Dominant	Roche 99th centile	£192	0.014	£14,126
Standard Tn	£3068	11.489				Abbott strategy	£43	–0.054	Dominated
RR re-infarction (untreated vs. treated) = 1.28									
Abbott 99th centile	£2788	11.532	–£275	0.036	Dominant				
Roche 99th centile	£2832	11.533	–£231	0.038	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2858	11.533	–£205	0.038	Dominant	Abbott 99th centile	£70	0.002	Dominated
Roche strategy	£2957	11.536	–£106	0.040	Dominant	Abbott 99th centile	£169	0.004	Extendedly dominated
Abbott strategy	£3025	11.544	–£38	0.048	Dominant	Abbott 99th centile	£237	0.012	£19,764
Standard Tn	£3063	11.496				Abbott strategy	£38	–0.048	Dominated

Annual post-myocardial infarction mortality

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Annual post-MI mortality = 0.068									
Abbott 99th centile	£2779	11.509	–£276	0.036	Dominant				
Roche 99th centile	£2822	11.511	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2848	11.512	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2947	11.514	–£107	0.042	Dominant	Abbott 99th centile	£169	0.006	Extendedly dominated
Abbott strategy	£3015	11.523	–£39	0.050	Dominant	Abbott 99th centile	£237	0.014	£17,036
Standard Tn	£3054	11.472				Abbott strategy	£39	–0.050	Dominated
Annual post-MI mortality = 0.065									
Abbott 99th centile	£2799	11.551	–£276	0.036	Dominant				
Roche 99th centile	£2843	11.553	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2868	11.553	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2968	11.556	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3035	11.565	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,059
Standard Tn	£3075	11.515				Abbott strategy	£39	–0.050	Dominated

Annual mortality post-myocardial infarction after re-infarction

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Annual mortality post-MI with re-infarction = 0.137									
Abbott 99th centile	£2790	11.532	–£276	0.036	Dominant				
Roche 99th centile	£2834	11.535	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2859	11.535	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2958	11.538	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3026	11.546	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,091
Standard Tn	£3066	11.496				Abbott strategy	£39	–0.050	Dominated
Annual mortality post-MI with re-infarction = 0.146									
Abbott 99th centile	£2788	11.527	–£276	0.036	Dominant				
Roche 99th centile	£2831	11.529	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2857	11.530	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2956	11.533	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3024	11.541	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,005
Standard Tn	£3063	11.491				Abbott strategy	£39	–0.050	Dominated

Hazard ratio mortality (unstable angina compared with non-ST segment elevation myocardial infarction)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
HR mortality (UA vs. NSTEMI) = 1.053									
Abbott 99th centile	£2740	11.363	–£276	0.036	Dominant				
Roche 99th centile	£2783	11.365	–£232	0.038	Dominant	Abbott 99th centile	£44	0.003	Extendedly dominated
Beckman 99th centile	£2809	11.366	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2908	11.369	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£2976	11.377	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,051
Standard Tn	£3015	11.327				Abbott strategy	£39	–0.050	Dominated
HR mortality (UA vs. NSTEMI) = 0.581									
Abbott 99th centile	£2835	11.685	–£275	0.037	Dominant				
Roche 99th centile	£2879	11.688	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2904	11.688	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£3003	11.691	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3071	11.699	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,044
Standard Tn	£3111	11.649				Abbott strategy	£39	–0.050	Dominated

Relative risk mortality (untreated compared with treated acute myocardial infarction)

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
RR mortality (untreated vs. treated AMI) = 3.908									
Abbott 99th centile	£2757	11.505	–£274	0.042	Dominant				
Roche 99th centile	£2812	11.516	–£219	0.053	Dominant	Abbott 99th centile	£56	0.012	£4755
Beckman 99th centile	£2845	11.522	–£186	0.059	Dominant	Roche 99th centile	£33	0.006	£5714
Roche strategy	£2945	11.526	–£85	0.063	Dominant	Beckman 99th centile	£101	0.004	Extendedly dominated
Abbott strategy	£3022	11.541	–£9	0.078	Dominant	Beckman 99th centile	£177	0.019	£9476
Standard Tn	£3031	11.463				Abbott strategy	£9	–0.078	Dominated
RR mortality (untreated vs. treated AMI) = 0.901									
Abbott 99th centile	£2804	11.542	–£276	0.034	Dominant				
Roche 99th centile	£2842	11.540	–£238	0.032	Dominant	Abbott 99th centile	£38	–0.002	Dominated
Beckman 99th centile	£2865	11.537	–£216	0.029	Dominant	Abbott 99th centile	£60	–0.004	Dominated
Roche strategy	£2963	11.540	–£118	0.032	Dominant	Abbott 99th centile	£159	–0.002	Dominated
Abbott strategy	£3027	11.545	–£54	0.037	Dominant	Abbott 99th centile	£223	0.003	£69,543
Standard Tn	£3081	11.508				Abbott strategy	£54	–0.037	Dominated

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Appendix 7 Subgroup analyses (base case)

Deterministic base case

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2257	11.734	–£440	–0.015	£28,870				
Roche 99th centile	£2301	11.740	–£396	–0.010	£41,233	Abbott 99th centile	£44	0.006	£7777
Beckman 99th centile	£2327	11.743	–£370	–0.006	£58,988	Roche 99th centile	£26	0.003	£7777
Roche strategy	£2426	11.744	–£271	–0.006	£48,559	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2493	11.748	–£204	–0.002	£124,391	Beckman 99th centile	£167	0.005	£35,904
Standard Tn	£2697	11.749				Abbott strategy	£204	0.002	£124,391

Age and sex subgroups

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Females *Age = 45 years*									
Abbott 99th centile	£2087	12.853	–£443	–0.016	£27,038				
Roche 99th centile	£2132	12.859	–£398	–0.010	£38,540	Abbott 99th centile	£45	0.006	£7414
Beckman 99th centile	£2158	12.863	–£372	–0.007	£55,060	Roche 99th centile	£27	0.004	£7414
Roche strategy	£2258	12.864	–£272	–0.006	£45,357	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2326	12.868	–£204	–0.002	£115,910	Beckman 99th centile	£168	0.005	£33,583
Standard Tn	£2530	12.870				Abbott strategy	£204	0.002	£115,910

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Age = 55 years									
Abbott 99th centile	£2093	10.615	–£443	–0.016	£28,189				
Roche 99th centile	£2138	10.620	–£398	–0.010	£40,181	Abbott 99th centile	£45	0.006	Extendedly dominated
Beckman 99th centile	£2164	10.624	–£372	–0.006	£57,405	Abbott 99th centile	£71	0.009	£7728
Roche strategy	£2263	10.624	–£272	–0.006	£47,288	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2332	10.629	–£204	–0.002	£120,850	Beckman 99th centile	£168	0.005	£35,013
Standard Tn	£2536	10.630				Abbott strategy	£204	0.002	£120,850
Age = 65 years									
Abbott 99th centile	£2087	8.193	–£443	–0.015	£29,368				
Roche 99th centile	£2132	8.199	–£398	–0.010	£41,866	Abbott 99th centile	£45	0.006	Extendedly dominated
Beckman 99th centile	£2158	8.202	–£372	–0.006	£59,816	Abbott 99th centile	£71	0.009	£8044
Roche strategy	£2258	8.203	–£272	–0.006	£49,272	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2326	8.207	–£204	–0.002	£125,935	Beckman 99th centile	£167	0.005	£36,479
Standard Tn	£2530	8.208				Abbott strategy	£204	0.002	£125,935
Age = 75 years									
Abbott 99th centile	£2037	5.640	–£442	–0.013	£32,776				
Roche 99th centile	£2082	5.645	–£398	–0.009	£46,745	Abbott 99th centile	£45	0.005	Extendedly dominated
Beckman 99th centile	£2108	5.648	–£371	–0.006	£66,808	Abbott 99th centile	£71	0.008	£8942
Roche strategy	£2207	5.649	–£272	–0.005	£55,024	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2276	5.652	–£204	–0.001	£140,710	Beckman 99th centile	£167	0.004	£40,725
Standard Tn	£2480	5.654				Abbott strategy	£204	0.001	£140,710

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Age = 85 years									
Abbott 99th centile	£1826	3.107	–£437	–0.007	£59,890				
Roche 99th centile	£1869	3.110	–£394	–0.005	£85,736	Abbott 99th centile	£43	0.003	Extendedly dominated
Beckman 99th centile	£1894	3.112	–£369	–0.003	£122,857	Abbott 99th centile	£68	0.004	£15,793
Roche strategy	£1993	3.112	–£270	–0.003	£101,053	Beckman 99th centile	£99	0.000	Extendedly dominated
Abbott strategy	£2059	3.114	–£203	–0.001	£259,592	Beckman 99th centile	£166	0.002	£74,597
Standard Tn	£2263	3.115				Abbott strategy	£203	0.001	£259,592
Males *Age = 45 years*									
Abbott 99th centile	£2404	14.047	–£438	–0.015	£28,815				
Roche 99th centile	£2447	14.053	–£395	–0.010	£41,214	Abbott 99th centile	£43	0.006	£7660
Beckman 99th centile	£2472	14.056	–£370	–0.006	£59,021	Roche 99th centile	£25	0.003	£7660
Roche strategy	£2571	14.057	–£271	–0.006	£48,561	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2638	14.061	–£204	–0.002	£124,616	Beckman 99th centile	£166	0.005	£35,870
Standard Tn	£2842	14.062				Abbott strategy	£204	0.002	£124,616
Age = 55 years									
Abbott 99th centile	£2407	11.852	–£438	–0.014	£30,338				
Roche 99th centile	£2450	11.857	–£395	–0.009	£43,396	Abbott 99th centile	£43	0.005	Extendedly dominated
Beckman 99th centile	£2476	11.860	–£370	–0.006	£62,149	Abbott 99th centile	£68	0.008	£8059
Roche strategy	£2575	11.861	–£271	–0.005	£51,134	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2642	11.865	–£204	–0.002	£131,231	Beckman 99th centile	£166	0.004	£37,768
Standard Tn	£2845	11.866				Abbott strategy	£204	0.002	£131,231

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Age = 65 years									
Abbott 99th centile	£2371	9.384	–£438	–0.013	£32,627				
Roche 99th centile	£2413	9.389	–£395	–0.008	£46,682	Abbott 99th centile	£43	0.005	Extendedly dominated
Beckman 99th centile	£2439	9.392	–£369	–0.006	£66,867	Abbott 99th centile	£68	0.008	£8647
Roche strategy	£2538	9.392	–£270	–0.005	£55,011	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2605	9.396	–£203	–0.001	£141,222	Beckman 99th centile	£166	0.004	£40,624
Standard Tn	£2808	9.397				Abbott strategy	£203	0.001	£141,222
Age = 75 years									
Abbott 99th centile	£2253	6.574	–£437	–0.011	£39,186				
Roche 99th centile	£2295	6.578	–£394	–0.007	£56,106	Abbott 99th centile	£42	0.004	Extendedly dominated
Beckman 99th centile	£2320	6.581	–£369	–0.005	£80,406	Abbott 99th centile	£68	0.007	£10,317
Roche strategy	£2419	6.581	–£270	–0.004	£66,133	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2486	6.584	–£203	–0.001	£169,919	Beckman 99th centile	£166	0.003	£48,814
Standard Tn	£2689	6.585				Abbott strategy	£203	0.001	£169,919
Age = 85 years									
Abbott 99th centile	£1940	3.634	–£429	–0.004	£114,585				
Roche 99th centile	£1980	3.635	–£389	–0.002	£164,917	Abbott 99th centile	£40	0.001	Extendedly dominated
Beckman 99th centile	£2004	3.636	–£366	–0.002	£237,203	Abbott 99th centile	£63	0.002	£28,711
Roche strategy	£2102	3.636	–£267	–0.001	£194,744	Beckman 99th centile	£99	0.000	Extendedly dominated
Abbott strategy	£2167	3.637	–£203	0.000	£503,476	Beckman 99th centile	£163	0.001	£143,225
Standard Tn	£2369	3.638				Abbott strategy	£203	0.000	£503,476

Subgroup with history of previous non-ST segment elevation myocardial infarction[a]

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£4643	5.764	–£472	–0.019	£25,031				
Roche 99th centile	£4699	5.771	–£417	–0.012	£35,017	Abbott 99th centile	£56	0.007	Extendedly dominated
Beckman 99th centile	£4732	5.775	–£384	–0.008	£49,358	Abbott 99th centile	£89	0.011	£7994
Roche strategy	£4834	5.776	–£281	–0.007	£40,639	Beckman 99th centile	£103	0.001	Extendedly dominated
Abbott strategy	£4910	5.781	–£205	–0.002	£101,225	Beckman 99th centile	£178	0.006	£31,052
Standard Tn	£5115	5.783				Abbott strategy	£205	0.002	£101,225

a Based on an AMI prevalence of 20% (see *Appendix 9*).

Myocardial infarction prevalence

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
MI prevalence = 1%									
No testing	£576	12.891	–£439	–0.005	£96,456				
Abbott 99th centile	£687	12.894	–£329	–0.001	£366,354	No testing	£111	0.004	Extendedly dominated
Roche 99th centile	£690	12.895	–£326	–0.001	£576,522	No testing	£113	0.004	Extendedly dominated
Beckman 99th centile	£691	12.895	–£324	0.000	£878,364	No testing	£115	0.004	£27,409
Roche strategy	£774	12.895	–£241	0.000	£734,155	Beckman 99th centile	£83	0.000	Extendedly dominated
Abbott strategy	£813	12.895	–£202	0.000	£2,097,914	Beckman 99th centile	£122	0.000	£447,934
Standard Tn	£1016	12.895				Abbott strategy	£202	0.000	£2,097,914
MI prevalence = 5%									
No testing	£855	12.586	–£581	–0.023	£25,513				
Abbott 99th centile	£1079	12.604	–£356	–0.004	£79,492	No testing	£224	0.018	Extendedly dominated
Roche 99th centile	£1092	12.606	–£344	–0.003	£121,526	No testing	£237	0.020	Extendedly dominated
Beckman 99th centile	£1100	12.607	–£336	–0.002	£181,894	No testing	£245	0.021	£11,703
Roche strategy	£1187	12.607	–£249	–0.002	£151,398	Beckman 99th centile	£87	0.000	Extendedly dominated
Abbott strategy	£1233	12.608	–£203	0.000	£420,420	Beckman 99th centile	£133	0.001	£97,709
Standard Tn	£1436	12.609				Abbott strategy	£203	0.000	£420,420

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
MI prevalence = 10%									
No testing	£1204	12.205	–£758	–0.046	£16,645				
Abbott 99th centile	£1570	12.242	–£391	–0.009	£43,635	No testing	£366	0.037	Extendedly dominated
Roche 99th centile	£1596	12.245	–£366	–0.006	£64,651	No testing	£392	0.040	Extendedly dominated
Beckman 99th centile	£1611	12.247	–£350	–0.004	£94,836	No testing	£407	0.042	£9740
Roche strategy	£1703	12.247	–£258	–0.003	£78,554	Beckman 99th centile	£92	0.000	Extendedly dominated
Abbott strategy	£1758	12.250	–£203	–0.001	£210,733	Beckman 99th centile	£147	0.003	£53,931
Standard Tn	£1961	12.251				Abbott strategy	£203	0.001	£210,733
MI prevalence = 20%									
No testing	£1900	11.443	–£1112	–0.091	£12,211				
Abbott 99th centile	£2551	11.516	–£461	–0.018	£25,706	No testing	£651	0.073	Extendedly dominated
Roche 99th centile	£2603	11.523	–£410	–0.011	£36,214	No testing	£702	0.080	Extendedly dominated
Beckman 99th centile	£2633	11.527	–£379	–0.007	£51,306	No testing	£733	0.084	£8759
Roche strategy	£2735	11.528	–£277	–0.007	£42,131	Beckman 99th centile	£102	0.001	Extendedly dominated
Abbott strategy	£2808	11.532	–£204	–0.002	£105,889	Beckman 99th centile	£175	0.005	£32,042
Standard Tn	£3012	11.534				Abbott strategy	£204	0.002	£105,889
MI prevalence = 30%									
No testing	£2597	10.681	–£1466	–0.137	£10,733				
Abbott 99th centile	£3532	10.791	–£531	–0.027	£19,730	No testing	£935	0.110	Extendedly dominated
Roche 99th centile	£3610	10.801	–£454	–0.017	£26,735	No testing	£1012	0.120	Extendedly dominated
Beckman 99th centile	£3655	10.807	–£408	–0.011	£36,797	No testing	£1058	0.125	£8431
Roche strategy	£3767	10.808	–£296	–0.010	£29,991	Beckman 99th centile	£112	0.001	Extendedly dominated
Abbott strategy	£3858	10.815	–£205	–0.003	£70,942	Beckman 99th centile	£203	0.008	£24,745
Standard Tn	£4063	10.818				Abbott strategy	£205	0.003	£70,942

Appendix 8 Subgroup analyses (secondary analysis)

Deterministic secondary analysis

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Abbott 99th centile	£2789	11.530	–£276	0.036	Dominant				
Roche 99th centile	£2832	11.532	–£232	0.039	Dominant	Abbott 99th centile	£44	0.002	Extendedly dominated
Beckman 99th centile	£2858	11.532	–£206	0.039	Dominant	Abbott 99th centile	£69	0.003	Extendedly dominated
Roche strategy	£2957	11.535	–£107	0.042	Dominant	Abbott 99th centile	£168	0.006	Extendedly dominated
Abbott strategy	£3025	11.543	–£39	0.050	Dominant	Abbott 99th centile	£236	0.014	£17,047
Standard Tn	£3064	11.493				Abbott strategy	£39	–0.050	Dominated

Age and sex subgroups

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Females *Age = 45 years*									
Abbott 99th centile	£2602	12.547	–£276	0.042	Dominant				
Roche 99th centile	£2647	12.549	–£231	0.044	Dominant	Abbott 99th centile	£45	0.003	Extendedly dominated
Beckman 99th centile	£2673	12.550	–£205	0.044	Dominant	Abbott 99th centile	£71	0.003	Extendedly dominated
Roche strategy	£2773	12.553	–£105	0.048	Dominant	Abbott 99th centile	£170	0.006	Extendedly dominated
Abbott strategy	£2841	12.562	–£37	0.057	Dominant	Abbott 99th centile	£239	0.015	£16,023
Standard Tn	£2878	12.505				Abbott strategy	£37	–0.057	Dominated

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Age = 55 years									
Abbott 99th centile	£2605	10.407	–£276	0.034	Dominant				
Roche 99th centile	£2650	10.410	–£231	0.037	Dominant	Abbott 99th centile	£45	0.003	£15,224
Beckman 99th centile	£2676	10.410	–£205	0.038	Dominant	Roche 99th centile	£26	0.001	Extendedly dominated
Roche strategy	£2776	10.413	–£105	0.040	Dominant	Roche 99th centile	£126	0.003	Extendedly dominated
Abbott strategy	£2844	10.421	–£37	0.048	Dominant	Roche 99th centile	£194	0.011	£17,150
Standard Tn	£2881	10.373				Abbott strategy	£37	–0.048	Dominated
Age = 65 years									
Abbott 99th centile	£2592	8.089	–£276	0.025	Dominant				
Roche 99th centile	£2637	8.092	–£232	0.029	Dominant	Abbott 99th centile	£45	0.003	£13,064
Beckman 99th centile	£2663	8.094	–£205	0.030	Dominant	Roche 99th centile	£26	0.001	Extendedly dominated
Roche strategy	£2762	8.096	–£106	0.032	Dominant	Roche 99th centile	£126	0.003	Extendedly dominated
Abbott strategy	£2831	8.103	–£37	0.039	Dominant	Roche 99th centile	£194	0.010	£18,999
Standard Tn	£2868	8.064				Abbott strategy	£37	–0.039	Dominated
Age = 75 years									
Abbott 99th centile	£2521	5.618	–£278	0.015	Dominant				
Roche 99th centile	£2565	5.621	–£234	0.019	Dominant	Abbott 99th centile	£44	0.004	£12,392
Beckman 99th centile	£2592	5.623	–£207	0.021	Dominant	Roche 99th centile	£26	0.002	£16,407
Roche strategy	£2691	5.625	–£108	0.022	Dominant	Beckman 99th centile	£99	0.002	Extendedly dominated
Abbott strategy	£2759	5.630	–£40	0.028	Dominant	Beckman 99th centile	£168	0.007	£24,020
Standard Tn	£2799	5.602				Abbott strategy	£40	–0.028	Dominated

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Age = 85 years									
Abbott 99th centile	£2250	3.104	–£289	0.002	Dominant				
Roche 99th centile	£2292	3.106	–£247	0.004	Dominant	Abbott 99th centile	£42	0.002	£21,140
Beckman 99th centile	£2317	3.107	–£222	0.005	Dominant	Roche 99th centile	£25	0.001	£26,911
Roche strategy	£2416	3.108	–£123	0.006	Dominant	Beckman 99th centile	£99	0.001	Extendedly dominated
Abbott strategy	£2483	3.111	–£56	0.009	Dominant	Beckman 99th centile	£166	0.004	£45,709
Standard Tn	£2539	3.102				Abbott strategy	£56	–0.009	Dominated
Males *Age = 45 years*									
Abbott 99th centile	£2958	13.801	–£275	0.042	Dominant				
Roche 99th centile	£3000	13.803	–£233	0.044	Dominant	Abbott 99th centile	£43	0.002	Extendedly dominated
Beckman 99th centile	£3026	13.803	–£207	0.044	Dominant	Abbott 99th centile	£68	0.002	Dominated
Roche strategy	£3125	13.806	–£108	0.047	Dominant	Abbott 99th centile	£167	0.005	Extendedly dominated
Abbott strategy	£3192	13.815	–£41	0.056	Dominant	Abbott 99th centile	£235	0.014	£16,897
Standard Tn	£3233	13.759				Abbott strategy	£41	–0.056	Dominated
Age = 55 years									
Abbott 99th centile	£2954	11.689	–£276	0.035	Dominant				
Roche 99th centile	£2997	11.691	–£233	0.037	Dominant	Abbott 99th centile	£43	0.002	Extendedly dominated
Beckman 99th centile	£3022	11.691	–£208	0.037	Dominant	Abbott 99th centile	£68	0.002	Dominated
Roche strategy	£3121	11.694	–£109	0.040	Dominant	Abbott 99th centile	£167	0.005	Extendedly dominated
Abbott strategy	£3188	11.702	–£41	0.048	Dominant	Abbott 99th centile	£234	0.013	£17,836
Standard Tn	£3230	11.654				Abbott strategy	£41	–0.048	Dominated

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Age = 65 years									
Abbott 99th centile	£2902	9.306	–£276	0.026	Dominant				
Roche 99th centile	£2945	9.309	–£234	0.029	Dominant	Abbott 99th centile	£43	0.003	£16,877
Beckman 99th centile	£2970	9.310	–£209	0.029	Dominant	Roche 99th centile	£25	0.001	Extendedly dominated
Roche strategy	£3069	9.312	–£110	0.032	Dominant	Roche 99th centile	£124	0.003	Extendedly dominated
Abbott strategy	£3136	9.319	–£42	0.039	Dominant	Roche 99th centile	£191	0.010	£19,851
Standard Tn	£3179	9.280				Abbott strategy	£42	–0.039	Dominated
Age = 75 years									
Abbott 99th centile	£2752	6.560	–£278	0.017	Dominant				
Roche 99th centile	£2795	6.563	–£236	0.019	Dominant	Abbott 99th centile	£42	0.002	£16,994
Beckman 99th centile	£2819	6.563	–£211	0.020	Dominant	Roche 99th centile	£25	0.001	Extendedly dominated
Roche strategy	£2918	6.565	–£112	0.022	Dominant	Roche 99th centile	£124	0.003	Extendedly dominated
Abbott strategy	£2985	6.570	–£45	0.027	Dominant	Roche 99th centile	£191	0.008	£25,149
Standard Tn	£3030	6.543				Abbott strategy	£45	–0.027	Dominated
Age = 85 years									
Abbott 99th centile	£2374	3.631	–£283	0.006	Dominant				
Roche 99th centile	£2414	3.631	–£244	0.007	Dominant	Abbott 99th centile	£40	0.001	Extendedly dominated
Beckman 99th centile	£2437	3.631	–£220	0.007	Dominant	Abbott 99th centile	£63	0.001	Extendedly dominated
Roche strategy	£2536	3.632	–£122	0.007	Dominant	Abbott 99th centile	£162	0.001	Extendedly dominated
Abbott strategy	£2601	3.634	–£57	0.010	Dominant	Abbott 99th centile	£227	0.003	£66,418
Standard Tn	£2657	3.624				Abbott strategy	£57	–0.010	Dominated

Myocardial infarction prevalence

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
MI prevalence = 1%									
No testing	£1072	12.546	–£439	–0.005	£96,456				
Abbott 99th centile	£1405	12.619	–£106	0.068	Dominant	No testing	£333	0.073	£4563
Roche 99th centile	£1407	12.615	–£104	0.064	Dominant	Abbott 99th centile	£2	–0.004	Dominated
Beckman 99th centile	£1408	12.611	–£103	0.061	Dominant	Abbott 99th centile	£3	–0.008	Dominated
Roche strategy	£1492	12.614	–£20	0.064	Dominant	Abbott 99th centile	£87	–0.005	Dominated
Standard Tn	£1511	12.550				Abbott 99th centile	£106	–0.068	Dominated
Abbott strategy	£1531	12.620	£20	0.070	£290	Abbott 99th centile	£126	0.001	£109,991
MI prevalence = 5%									
No testing	£1316	12.265	–£581	–0.023	£25,513				
Abbott 99th centile	£1747	12.348	–£150	0.060	Dominant	No testing	£431	0.083	£5209
Roche 99th centile	£1759	12.346	–£137	0.058	Dominant	Abbott 99th centile	£13	–0.002	Dominated
Beckman 99th centile	£1766	12.343	–£130	0.055	Dominant	Abbott 99th centile	£20	–0.005	Dominated
Roche strategy	£1854	12.346	–£43	0.058	Dominant	Abbott 99th centile	£107	–0.002	Dominated
Standard Tn	£1897	12.288				Abbott 99th centile	£150	–0.060	Dominated
Abbott strategy	£1900	12.352	£4	0.064	£61	Abbott 99th centile	£154	0.004	£35,574

			Compared with standard Tn			Compared with next best strategy			
Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs	Comparator	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
MI prevalence = 10%									
No testing	£1623	11.913	–£758	–0.046	£16,645				
Abbott 99th centile	£2178	12.008	–£203	0.050	Dominant	No testing	£554	0.095	£5820
Roche 99th centile	£2203	12.008	–£178	0.049	Dominant	Abbott 99th centile	£25	0.000	Dominated
Beckman 99th centile	£2218	12.006	–£163	0.048	Dominant	Abbott 99th centile	£40	–0.002	Dominated
Roche strategy	£2311	12.009	–£71	0.051	Dominant	Abbott 99th centile	£133	0.001	Extendedly dominated
Abbott strategy	£2366	12.017	–£15	0.058	Dominant	Abbott 99th centile	£188	0.008	£22,684
Standard Tn	£2381	11.958				Abbott strategy	£15	–0.058	Dominated
MI prevalence = 20%									
No testing	£2247	11.202	–£1112	–0.091	£12,211				
Abbott 99th centile	£3053	11.324	–£306	0.031	Dominant	No testing	£806	0.122	£6625
Roche 99th centile	£3104	11.327	–£255	0.034	Dominant	Abbott 99th centile	£51	0.004	£14,063
Beckman 99th centile	£3135	11.328	–£224	0.035	Dominant	Roche 99th centile	£30	0.001	Extendedly dominated
Roche strategy	£3237	11.331	–£122	0.038	Dominant	Roche 99th centile	£132	0.004	Extendedly dominated
Abbott strategy	£3310	11.340	–£49	0.047	Dominant	Roche 99th centile	£206	0.013	£16,319
Standard Tn	£3359	11.293				Abbott strategy	£49	–0.047	Dominated
MI prevalence = 30%									
No testing	£2880	10.484	–£1466	–0.137	£10,733				
Abbott 99th centile	£3942	10.634	–£404	0.013	Dominant	No testing	£1062	0.149	£7109
Roche 99th centile	£4019	10.641	–£327	0.020	Dominant	Abbott 99th centile	£77	0.008	£10,278
Beckman 99th centile	£4065	10.645	–£281	0.024	Dominant	Roche 99th centile	£46	0.004	£12,899
Roche strategy	£4177	10.648	–£169	0.027	Dominant	Beckman 99th centile	£112	0.003	Extendedly dominated
Abbott strategy	£4268	10.658	–£78	0.037	Dominant	Beckman 99th centile	£203	0.013	£15,410
Standard Tn	£4346	10.621				Abbott strategy	£78	–0.037	Dominated

Appendix 9 Subgroup analyses based on accuracy and acute myocardial infarction prevalence (available for only the Roche 99th centile test)

Base case	MI prevalence[a]	Roche 99th centile		Standard Tn		Increments		
		Costs	QALYs	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts/ΔQALYs
Base case	17%	£2301	11.740	£2697	11.749	–£396	–0.010	£41,233
Age ≤ 70 years	28%	£3411	10.946	£3853	10.961	–£442	–0.015	£28,633
Age > 70 years	10%	£1550	6.274	£1880	6.275	–£330	–0.001	£355,571
With pre-existing CAD	20%	£2641	11.528	£3012	11.534	–£371	–0.006	£58,509
Without pre-existing CAD	16%	£2236	11.816	£2592	11.821	–£356	–0.004	£80,454
Symptom onset < 3 hours	22%	£2726	11.369	£3222	11.391	–£496	–0.022	£22,111
Symptom onset > 3 hours	13%	£1929	12.032	£2277	12.036	–£348	–0.003	£103,107
Symptom onset < 3 hours	17%	£2241	11.732	£2697	11.749	–£456	–0.017	£26,327
Symptom onset > 3 hours	17%	£2341	11.745	£2697	11.749	–£356	–0.004	£80,677
Base case	17%	£2832	11.532	£3064	11.493	–£232	0.039	Dominant
Age ≤ 70 years[b]	28%	£3839	10.780	£4148	10.756	–£310	0.024	Dominant
Age > 70 years[c]	10%	£2111	6.245	£2259	6.222	–£148	0.023	Dominant
With pre-existing CAD	20%	£3142	11.325	£3359	11.293	–£217	0.031	Dominant
Without pre-existing CAD	16%	£2778	11.604	£2967	11.560	–£189	0.044	Dominant
Symptom onset < 3 hours	22%	£3209	11.180	£3556	11.159	–£347	0.021	Dominant
Symptom onset > 3 hours	13%	£2503	11.806	£2673	11.760	–£171	0.046	Dominant
Symptom onset < 3 hours	17%	£2772	11.524	£3064	11.493	–£292	0.031	Dominant
Symptom onset > 3 hours	17%	£2873	11.535	£3064	11.493	–£192	0.042	Dominant

a The two studies presenting data on subgroups[39,67] were both conducted in patients in whom NSTEMI had not been excluded. They were not at specifically high or low risk of AMI. We calibrated the prevalence (obtained from these studies) in the subgroup to be adapted to a population with a prevalence of 17% (see below).
b Average age = 53 (base case value) years.
c Average age = 75 years.

Acute myocardial infarction prevalence in subgroups

Subgroup	Prevalence of AMI (*x*)	Prevalence of AMI in whole population from subgroups were derived (*y*)	Prevalence assuming population prevalence of 17% (multiple *x*y*/17)	Source
Age ≤ 70 years	24%	15%	28%	APACE[39,52]
Age > 70 years	9%	15%	10%	APACE[39,52]
Patients with CAD	18%	16%	20%	APACE[39,52]
Patients without CAD	14%	16%	16%	APACE[39,52]
< 3 hours from symptoms[67]	24%	18%	22%	APACE,[39] Body (2011)[67]
> 3 hours from symptoms[67]	14%	18%	13%	APACE,[39] Body (2011)[67]
< 3 hours from symptoms[39]	21%	21%	17%	APACE,[39] Body (2011)[67]
> 3 hours from symptoms[39]	21%	21%	17%	APACE,[39] Body (2011)[67]

Appendix 10 National Institute for Health and Care Excellence guidance relevant to the management of suspected acute coronary syndrome

- MI – secondary prevention: secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline CG172 (2013). URL: http://guidance.nice.org.uk/CG172. Date for review: not stated.
- Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE clinical guideline CG95 (2010). URL: www.nice.org.uk/guidance/CG95. Reviewed March 2013, review recommended.
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